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Review

A Review of the Principles of Radiological Assessment of Skeletal Dysplasias

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ABSTRACT

There are more than 450 well-characterized skeletal dysplasias classified primarily on the basis of clinical, radiographic, and molecular criteria. In the latest 2010 revision of the Nosology and Classification of Genetic Skeletal Disorders, an increase from 372 to 456 disorders had occurred in the four years since the classification was last revisited in 2007. These entities in total represent about 5% of children with birth defects. An accurate diagnosis of a skeletal dysplasia is still based on detailed evaluation of clinical and radiographic [as well as chondro-osseous] findings. Regardless of the specific diagnosis, skeletal dysplasias in general share clinical and radiological findings helping us to group them in several ways. This review aims to outline the diagnostic approach to disproportionate short stature with special emphasis on radiological findings.

Key words: Skeletal dysplasia, disproportionate short stature, radiology

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Introduction

Skeletal dysplasias are disorders associated with a generalized abnormality in the skeleton. Although individually rare, the overall birth incidence is estimated to be 1/5000 live births (1). Today, there are more than 450 well-characterized skeletal dysplasias classified primarily on the basis of clinical, radiographic, and molecular criteria (2). Half a century ago, in the 1960s, individuals with disproportionate short stature were diagnosed either as achondroplasia (short-limbed dwarfism) or Morquio syndrome (short-trunked dwarfism). In time, delineation of numerous entities not fitting these two "disorders" led experts to come up with a systematic approach. The "International Nomenclature of Constitutional Diseases of Bone" group, since its first publication in 1970, has intermittently classified these disorders (1970-1977-1983-1992-2001-2005-2009) (3). In the 1970s, the categories were purely clinical and descriptive. This later evolved into a combination of clinical, radiological and molecular knowledge as the pathogenetic mechanisms of various entities have been revealed. In the latest 2010 revision of the Nosology and Classification of Genetic Skeletal Disorders, an increase from 372 to 456 disorders was noted in the four years since the classification was last revisited in 2007 (2,4). Of these conditions, 316 are associated with one or more of 226 different genes. This increase reflects the

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continuing delineation of unique phenotypes among short stature conditions, which in aggregate represent about 5% of children with birth defects (1). Some of the increase has also been driven by technological improvements in our ability to define the molecular genetic basis of these conditions, which is now known for 316 of the disorders (215 in the prior revision), with defects in 226 (140 previously) different genes. Table 1 provides a list of main groups in the latest published classification (2).

In daily practice however, clinicians dealing with patients with short stature may be confused with the molecular listings. It is therefore important to remember that an accurate diagnosis of a skeletal dysplasia is still based on detailed evaluation of clinical and radiographic [as well as chondro-osseous] findings. This review aims to outline the diagnostic approach to disproportionate short stature with special emphasis on radiological findings.

Clinical Evaluation

The accurate history regarding time of onset of short stature is essential prior to physical examination. Among the nearly 400 skeletal dysplasias, 100 or so have prenatal onset, while others may only present either as newborns or beyond 2 to 3 years of age (5). Individuals with disproportionate short stature are likely to be affected by a skeletal dysplasia. However, the abnormal proportions may not be readily recognizable. Therefore, whenever an individual presents with short stature, it is essential to measure body proportions. This should be done keeping in mind that some generalized bone mineralization abnormalities such as osteogenesis imperfects (OI), some osteosclerotic disorders, and hypophosphatasia may present with near normal proportions.

Anthropometric measurements such as upper/lower segment (U/L) ratio, sitting height, and arm span are routinely measured when a patient with short stature is evaluated. Sitting height is the measurement of head and trunk, and may be difficult to measure accurately due to the need of special equipment. The lower segment, however, is easier to measure (from symphysis pubis towards the floor medially to the heel). The upper segment can then be easily calculated by subtracting the lower segment from total height. Upper and lower segment measurements can be made in a standing or supine position. The mentioned ratios change with age. U/L ratio is 1.7 in the newborn; approximately 1.0 between ages 2-8 years; 0.95 as an adult. A short statured patient with short trunk will have decreased a U/L ratio, while an individual with normal trunk and relatively short limbs will have an increased U/L ratio (6).

Clinical evaluation also includes description of the limb involvement. Depending on the primarily involved segment of the limb, the condition can be described as rhizomelic (humerus and femur), mesomelic (radius, ulna, tibia and fibula) and acromelic (hands and feet). These descriptions help in differential diagnosis. It is noteworthy that a careful examination by an experienced clinical geneticist can sometimes narrow the list of dysmorphological entities to be considered even before the skeletal radiographs are analyzed (7).

Other clinical assessments such as immunological /hematological data as well as hair quality, cleft palate, eye abnormalities (myopia) and even internal organ abnormalities (cystic kidneys, hepatosplenomegaly) are important in skeletal dysplasia evaluation.

After obtaining a thorough family history, constructing a detailed pedigree and performing clinical examination, radiological assessment is likely to close the case in most skeletal dysplasias as many have distinctive radiological features in growing bones.

Radiological Assessment

Before giving details of the stepwise radiographic analysis for skeletal dysplasias; we would like to emphasize that a complete " genetic skeletal survey" is not necessary in patients with proportionate short stature, in which the differential diagnosis consists of constitutional delay, familial short stature, a small group of endocrinopathies and some dysmorphic syndromes. Their initial imaging assessment may warrant a left hand and wrist radiograph for bone age determination. This will protect children from unnecessary radiation exposure.

The "genetic skeletal survey" should include anteroposterior (AP), and lateral views of the skull, AP and lateral views of the entire spine, and AP views of the pelvis and all four extremities, with separate AP views of the hands and feet [A lateral view of the knee can be helpful to diagnose a recessive form of multiple epiphyseal dysplasia (MED) associated with multilayered patella] (7). In adult patients, it is mandatory to try to obtain prepubertal skeletal radiographs. Once the epiphyses have fused to the metaphyses, diagnosis may be very difficult. After obtaining the radiographs, a three-step assessment will be helpful in trying to make a specific diagnosis.

Step I (Assessment of Disproportion): An assessment of disproportion similar to the one made clinically is repeated looking at the radiographs. A quick look at the spine will readily help decide if there is platyspondyly leading to short-trunked disproportion. Similarly, looking at the

Table 1. Osteochondrodysplasias (Nosology and Classification of Genetic Skeletal Disorders: 2010 Revision)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein
1. FGFR3 group					
Thanatophoric dysplasia type 1 (TD1)	AD	187600	4p16.3	FGFR3	FGFR3
Thanatophoric dysplasia type 2 (TD2)	AD	187601	4p16.3	FGFR3	FGFR3
SADDAN (severe achondroplasia-developmental delay- acanthosis nigricans)	AD	See 134934	4p16.3	FGFR3	FGFR3
Achondroplasia	AD	100800	4p16.3	FGFR3	FGFR3
Hypochondroplasia	AD	146000	4p16.3	FGFR3	FGFR3
Hypochondroplasia-like dysplasia	AD, SP				
Camptodactyly, tall stature, and hearing loss syndrome (CATSHL)	AD	187600	4p16.3	FGFR3	FGFR3
2. Type 2 collagen group					
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
Hypochondrogenesis	AD	200610	12q13.1	COL2A1	Type 2 collagen
Spondyloepiphyseal dysplasia congenital (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
SED with metatarsal shortening (formerly Czech dysplasia)	AD	609162	12q13.1	COL2A1	Type 2 collagen
Stickler syndrome type 1 Stickler-like syndrome	AD	108300	12q13.1	COL2A1	Type 2 collagen
3. Type 11 collagen group					
Stickler syndrome type 2	AD	604841	1p21	COL11A1 alpha-1 chain	Type 11 collagen
Marshall syndrome	AD	154780	1p21	COL11A1 alpha-1 chain	Type 11 collagen
Fibrochondrogenesis	AR	228520	1p21	COL11A1 alpha-1 chain	Type 11 collagen
Otospondylomegaepiphyseal dysplasia (OSMED), recessive type	AR	215150	6p21.3	COL11A2	Type 11 collagen alpha-2 chain
Otospondylomegaepiphyseal dysplasia (OSMED), dominant type (Weissenbacher-Zweymüller syndrome, Stickler syndrome type 3)	AD	215150	6p21.3	COL11A2	Type 11 collagen alpha-2 chain
4. Sulphation disorders group					
Achondrogenesis type 1B (ACG1B)	AR	600972	5q32-33	DTDST	SLC26A2 sulfate transporter
Atelosteogenesis type 2 (AO2)	AR	256050	5q32-33	DTDST	SLC26A2 sulfate transporter
Diastrophic dysplasia (DTD)	AR	222600	5q32-33	DTDST	SLC26A2 sulfate transporter
MED, autosomal recessive type (rMED; EDM4)	AR	226900	5q32-33	DTDST	SLC26A2 sulfate transporter
SEMD, PAPSS2 type	AR	603005	10q23-q24	PAPSS2	PAPS-Synthetase 2

Table 1. (continued)

Chondrodysplasia with congenital joint dislocations, CHST3 type (recessive Larsen syndrome)	AR	608637	10q22.1	CHST3	Carbohydrate sulfotransferase 3; Chondroitin 6-sulfotransferase
Ehlers-Danlos syndrome, CHST14 type ("musculo-skeletal variant")	AR	601776	15q14	CHST14	Carbohydrate sulfotransferase 14; dermatan 4-sulfotransferase
5. Perlecan group					
Dyssegmental dysplasia, Silverman- Handmaker type	AR	224410	1q36-34	PLC (HSPG2)	Perlecan
Dyssegmental dysplasia, Roland-Desbuqois	AR	224400	1q36-34	PLC (HSPG2)	Perlecan
Schwartz-Jampel syndrome (myotonic chondrodystrophy)	AR	255800	1q36-34	PLC (HSPG2)	Perlecan
6. Aggrecan group					
SED, Kimberley type	AD	608361	15q26	AGC1	Aggrecan
SEMD, Aggrecan type	AR	612813	15q26	AGC1	Aggrecan
Familial osteochondritis dissecans	AD	165800	15q26	AGC1	Aggrecan
7. Filamin group and related disorders					
Frontometaphyseal dysplasia	XLD	305620	Xq28	FLNA	Filamin A
Osteodysplasty Melnick-Needles	XLD	309350	Xq28	FLNA	Filamin A
Otopalatodigital syndrome type 1 (OPD1)	XLD	311300	Xq28	FLNA	Filamin A
Otopalatodigital syndrome type 2 (OPD2)	XLD	304120	Xq28	FLNA	Filamin A
Atelosteogenesis type 1 (AO1)	AD	108720	3p14.3	FLNB	Filamin B
Atelosteogenesis type 3 (AO3)	AD	108721	3p14.3	FLNB	Filamin B
Larsen syndrome	AD	150250	3p14.3	FLNB	Filamin B
Spondylo-carpal-tarsal dysplasia	AR	272460	3p14.3	FLNB	Filamin B
Franck-ter-Haar syndrome	AR	249420	5q35.1	SH3PXD28	TKS4
Serpentine fibula-polycystic kidney syndrome	AD?	600330			
8. TRPV4 group					
Metatropic dysplasia	AD	156530	12q24.1	TRPV4	Transient receptor potential cation channel, subfamily V, member 4
Spondyloepimetaphyseal dysplasia, Maroteaux type (Pseudo-Morquio syndrome type 2)	AD	184095	12q24.1	TRPV4	Transient receptor potential cation channel, subfamily V, member 4
Spondylometaphyseal dysplasia, Kozlowski type	AD	184252	12q24.1	TRPV4	Transient receptor potential cation channel, subfamily V, member 4
Brachyolmia, autosomal dominant type	AD	113500	12q24.1	TRPV4	Transient receptor potential cation channel, subfamily V, member 4
Familial digital arthropathy with brachydactyly	AD	606835	12q24.1	TRPV4	Transient receptor potential cation channel, subfamily V, member 4
9. Short-rib dysplasias (with or without polydactyly) group					
Chondroectodermal dysplasia (Ellis-van Creveld)	AR	225500	4p16 4p16	EVC1 EVC2	EvC gene 1 EvC gene 2
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	AR	263510	11q22.3	DYNC2H1	Dynein, cytoplasmic 2, heavy chain 1
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	AR	263510	3q25.33	IFT80	Intraflagellar transport 80 (homolog of)
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	AR	263510			
SRP type 2 (Majewski)	AR	263520		NEK1	Nima related kinase 1
SRP type 4 (Beemer)	AR	269860			

Table 1. (continued)

Oral-Facial-Digital syndrome type 4 (Mohr-Majewski)	AR	258860			
Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	208500	11q22.3	DYNC2H1	Dynein, cytoplasmic 2, heavy chain 1
Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	208500	3q25.33	IFT80	Intraflagellar transport 80 (homolog of)
Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	208500			
Thoracolaryngopelvic dysplasia (Barnes)	AD	187760			
10. Multiple epiphyseal dysplasia and pseudoachondroplasia group					
Pseudoachondroplasia (PSACH)	AD	177170	19p12-13.1	COMP	COMP
Multiple epiphyseal dysplasia (MED) type 1 (EDM1)	AD	132400	19p13.1	COMP	COMP
Multiple epiphyseal dysplasia (MED) type 2 (EDM2)	AD	600204	1p32.2-33	COL9A2	Collagen 9 alpha-2 chain
Multiple epiphyseal dysplasia (MED) type 3 (EDM3)	AD	600969	20q13.3	COL9A3	Collagen 9 alpha-3 chain
Multiple epiphyseal dysplasia (MED) type 5 (EDM5)	AD	607078	2p23-24	MATN3	Matrilin 3
Multiple epiphyseal dysplasia (MED) type 6 (EDM6)	AD	120210	6q13	COL9A1	Collagen 9 alpha-1 chain
Multiple epiphyseal dysplasia (MED), other types					
Stickler syndrome, recessive type	AR	120210	6q13	COL9A1	Collagen 9 alpha-1 chain
Familial hip dysplasia (Beukes)	AD	142669	4q35		
Multiple epiphyseal dysplasia with microcephaly and nystagmus (Lowry-Wood)	AR	226960			
11. Metaphyseal dysplasias					
Metaphyseal dysplasia, Schmid type (MCS)	AD	156500	6q21-22.3	COL10A1	Collagen 10 alpha-1 chain
Cartilage-hair-hypoplasia (CHH; metaphyseal dysplasia, McKusick type)	AR	250250	9p13	RMRP	RNA component of RNAse H
Metaphyseal dysplasia, Jansen type	AD	156400	3p22-21.1	PTHR1	PTH/PTHrP receptor 1
Eiken dysplasia	AR	600002	3p22-22.1	PTHR1	PTH/PTHrP receptor 1
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman-Bodian-Diamond syndrome, SBDS)	AR	260400	7q11	SBDS	SBDS gene, function unclear
Metaphyseal anadysplasia type 1	AD,AR	309645	11q22	MMP13	Matrix metalloproteinase 13
Metaphyseal anadysplasia type 2	AR		20q13.12	MMP9	Matrix metalloproteinase 9
Metaphyseal dysplasia, Spahr type	AR	250400			
Metaphyseal acroscyphodysplasia (various types)	AR	250215			
Genochondromatosis (type1/type 2)	AD/SP	137360			
Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria	AR/SP	271550			
12. Spondylometaphyseal dysplasias (SMD)					
Spondyloenchondrodysplasia (SPENCD)	AR	271550	19p13.2	ACP5	Tartrate-resistant acid phosphatase (TRAP)
Odontochondrodysplasia (ODCD)	AR	184260			
Spondylometaphyseal dysplasia Kozlowski type	AD	184252			
Spondylometaphyseal dysplasia, Sutcliffe/corner fracture type	AD	184255			
SMD with severe genu valgum	AD	184253			
SMD with cone-rod dystrophy	AR	608940			
SMD with retinal degeneration, axial type	AR	602271			
Dysspondyloenchondromatosis	SP				
Cheiro-spondyloenchondromatosis	SP				

Table 1. (continued)

13. Spondylo-epi(-meta)physeal dysplasias (SE(M)D)					
Dyggve-Melchior-Clausen dysplasia (DMC)	AR	223800	18q12-21.1	DYM	Dymeclin
Immuno-osseous dysplasia (Schimke)	AR	242900	2q34-36	SMARCAL1	SWI/SNF-related regulator of chromatin subfamily A-like protein 1
SED Wolcott-Rallison type	AR	226980	2p12	EIF2AK3	Translation initiation f actor 2-alpha kinase-3
SEMD Matrilin type	AR	608728	2p23-p24	MATN3	Matrilin 3
SEMD Missouri type	AD	602111	11q22.3	MMP13	Matrix metalloproteinase 13
Metatropic dysplasia (various forms)	AD/AR	156530			
SED tarda, X-linked (SED-XL)	XLR	313400	Xp22	SEDL	Sedlin
SPONASTRIME dysplasia	AR	271510			
SEMD short limb - abnormal calcification type	AR	271665	1q23	DDR2	Discoidin domain receptor family, member2
SEMD with joint laxity (SEMD-JL) Beighton type	AR	271640			
Spondylo-megaepiphyseal-metaphyseal dysplasia (SMMD)	AR	613330	4p16.1	NKX3	NK3 Homeobox
Spondylodysplastic Ehlers-Danlos syndrome	AR	271510	11p.11.2	SLC39A13	Zinc transporter ZIP13
SEMD with joint laxity (SEMD-JL) leptodactylic or Hall type	AD	603546			
Platyspondyly (brachyolmia) with amelogenesis imperfecta	AR	601216			
Late onset SED, autosomal recessive type	AR	609223			
Brachyolmia, Hobaek, and Toledo types	AR	271530, 271630			
14. Severe spondylodysplastic dysplasias					
Achondrogenesis type 1A (ACG1A)	AR	200600	14q32.12	TRIP11	Golgi-microtubule-assocated protein, 210-kDa; GMAP210
SMD Sedaghatian type	AR	250220			
Severe SMD Sedaghatian-like	AR		7q11	SBDS	SBDS gene, function still unclear
Opsismodysplasia	AR	258480			
Schneckenbecken dysplasia	AR	269250	1p31.3	SLC35D1	Solute carrier family 35 member D1; UDP-glucuronic acid/UDP-N-acetylgalactosamine dual trasporter
15. Acromelic dysplasias					
Trichorhinophalangeal dysplasia types 1/3	AD	190350 190351	8q24	TRPS1	Zinc finger transcription factor
Trichorhinophalangeal dysplasia type 2 (Langer- Giedion)	AD	150230	8q24	TRPS1 EXT1	Zinc finger transcription factor Exostosin 1
Acrocapitofemoral dysplasia	AR	607778	2q33-q35	IHH	Indian hedgehog
Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1	AR	218330			
Cranioectodermal dysplasia (Levin-Sensenbrenner) type 2	AR	613610	2p24.1	WDR35	WD repeat-containig protein 35
Geleophysic dysplasia	AR	231050	9q34.2	ADAMTSL2	ADAMTS-like protein 2
Geleophysic dysplasia, other types	AR				
Acromicric dysplasia	AD	102370			
Acrodysostosis	AD	101800			
Angel-shaped phalangoepiphyseal dysplasia (ASPED)	AD	105835			
Acrolaryngeal dysplasia	AD				
Craniofacial conodysplasia	AD				
Familial digital arthropathy with brachydactyly	AD	606835			
Saldino-Mainzer dysplasia	AR	266920			

Table 1. (continued)

16. Acromesomelic dysplasias					
Acromesomelic dysplasia type Maroteaux	AR	602875	9p13-12	NPR2	Natriuretic peptide receptor 2
Grebe dysplasia	AR	200700	20q11.2	GDF5	Growth and differentiation factor 5
Fibular hypoplasia and complex brachydactyly (Du Pan)	AR	228900	20q11.2	GDF5	Growth and differentiation factor 5
Acromesomelic dysplasia with genital anomalies	AR	609441	4q23-24	BMPR1B	Bone morphogenetic protein receptor 1B
Acromesomelic dysplasia, Osebold-Remondini type	AD	112910			
17. Mesomelic and rhizo-mesomelic dysplasias					
Dyschondrosteosis (Leri-Weill)	Pseudo-AD	127300	Xpter-p22.32	SHOX	Short stature - homeobox gene
Langer type (homozygous dyschondrosteosis)	Pseudo-AR	249700	Xpter-p22.32	SHOX	Short stature - homeobox gene
Robinow syndrome, recessive type	AR	268310	9q22	ROR2	Receptor tyrosine kinase-like orphan receptor 2
Robinow syndrome, dominant type	AD	180700			
Mesomelic dysplasia, Korean type	AD		2q24-32		
Mesomelic dysplasia, Kantaputra type	AD	156232	2q24-32		
Mesomelic dysplasia, Nievergelt type	AD	163400			
Mesomelic dysplasia, Kozlowski-Reardon type	AR	249710			
Mesomelic dysplasia with acral synostoses (Verloes-David-Pfeiffer type)	AD	600383	8q13	SULF1 and SLCO5A1	Heparan sulfatase 6-O-endosulfatase 1 and solute carrier organic anion transporter family member 5A1
Mesomelic dysplasia, Savarirayan type (Triangular Tibia-Fibular Aplasia)	SP	605274			
18. Bent bones dysplasias					
Campomelic dysplasia (CD)	AD	114290	17q24.3-25.1	SOX9	SRY-box 9
Stüve-Wiedemann dysplasia	AR	601559	5p13.1	LIFR	Leukemia inhibitory factor receptor
Cumming syndrome		211890			
Kyphomelic dysplasia, several forms		211350			
Bent bones at birth can be seen in a variety of conditions, including Antley-Bixler syndrome, cartilage-hair hypoplasia, hypophosphatasia, osteogenesis imperfecta, dyssegmental dysplasia, and others					
19. Slender bone dysplasia Group					
3-M syndrome (3M1)	AR	273750	6p21.1	CUL7	Cullin 7
3-M syndrome (3M2)	AR	619921	2q35	PBSL1	Obscurin-like 1
Kenny-Caffey dysplasia type 1	AR	244460	1q42-q43	TBCE	tubulin-specific chaperone E
Kenny-Caffey dysplasia type 2	AD	127000			
Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1)	AR	210710	2q		
Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type)	AR	210720	21q	PCNT2	Pericentrin 2
Microcephalic osteodysplastic dysplasia, Saul-Wilson type	AR				
IMAGE syndrome (Intrauterine Growth Retardation, Metaphyseal Dysplasia, Adrenal Hypoplasia, and Genital Anomalies)	XL/AD	300290			

Table 1. (continued)

Osteocraniostenosis	SP	602361		
Hallermann-Streiff syndrome	AR	234100		
20. Dysplasias with multiple joint dislocations				
Desbuquois dysplasia (with accessory ossification center in digit 2)	AR	251450	17q25.3	CANT1
Desbuquois dysplasia with short metacarpals and elongated phalanges)	AR	251450	17q25.3	CANT1
DEsbuquois dysplasia (other variants with or without accessory ossification center)	AR			
Pseudodiastrophic dysplasia	AR	264180		

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extremities may help defining rhizomelia, mesomelia, and acromelia. It should be noted that these descriptive terms of limb segments may be more correct radiologically as the clinical visualization is accentuated by skin folds or other tissues rather than the length of the underlying bone. Rhizomelic chondrodysplasia punctata (CDP) is a good example of a rhizomelic skeletal dysplasia diagnosed with the additional radiological findings of punctate calcifications (stippling) and coronal clefted vertebrae (Figure 1). Mesomelia alone will suggest a long heterogeneous differential diagnosis list of mesomelic dysplasias. Presence of acromelia is important to recognize, as it may be an isolated finding. Presence of isolated acromelia may suggest skeletal dysplasias such as acromicric dysplasia, acrodysostosis, geleophysic dysplasia or nonskeletal dysplasias such as the brachydactylies. Brachydactyly type E, characterized by a short fourth metacarpal bone may support clinical or laboratory findings in Turner syndrome and pseudohypoparathyroidism, respectively. The absence of proportional acromelic shortening is also very important to remember in spondyloepiphyseal dysplasia congenita (and most forms of type II collagenopathies) (7).

Step II (Assessment of Epiphyseal/Metaphyseal/ Diaphyseal Ossification): Abnormal development of epiphyses, metaphyses, and diaphyses has given rise to the original nomenclature using those site names (Figure 2). An overall look at the radiological survey will suggest epiphyseal dysplasias by the presence of very small (delayed ossification) and/or irregularly ossified epiphyses (Figure 3a). If the metaphyses are widened, flared, and/or irregular, the diagnosis of a form of metaphyseal dysplasia is established (Figure 3b, 3c and Figure 4). Diaphyseal dysplasia is present when there is diaphyseal widening and/or cortical thickening or marrow space expansion or restriction. Isolated vertebral involvement without changes in the growth plate region in a patient with short-trunked

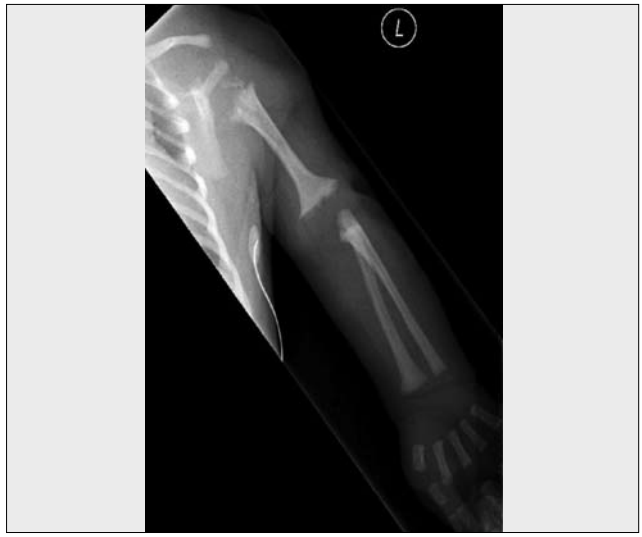

Figure 1. Rhizomelic chondrodysplasia punctata. Note shortness of humerus (rhizomelia and punctate calcifications in proximal humerus)

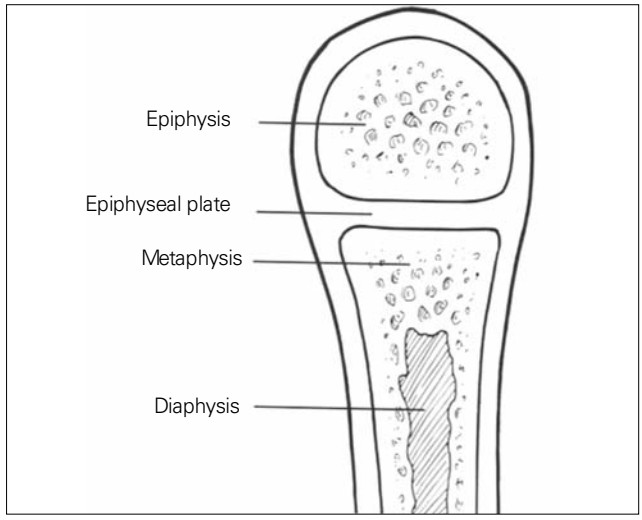

Figure 2. Key areas of the growing bone

short stature should suggest brachyolmia (Figure 5a and 5b). Figure 3 helps to combine the aforementioned skeletal involvement, such as forms of spondyloepiphyseal dysplasia and the group of spondylo-epi-(meta)-physeal

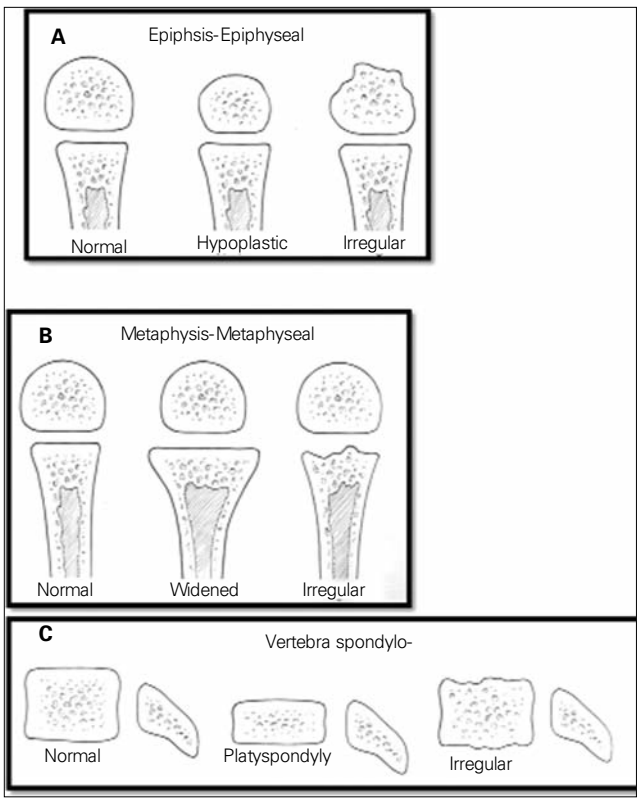

Figure 3. a,b,c. Radiographic manifestations of the dysplasias

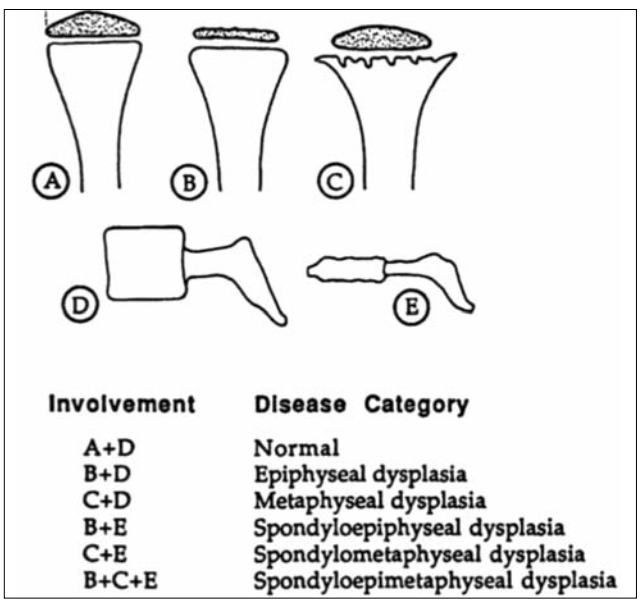

Figure 4. Radiographic abnormalities helpful in classification of skeletal dysplasias

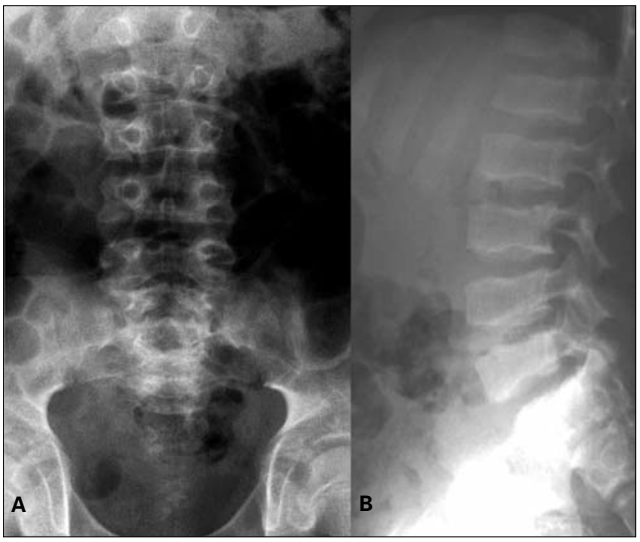

Figure 5. a,b. Brachyolmia. Note platyspondyly and overfaced pedicles

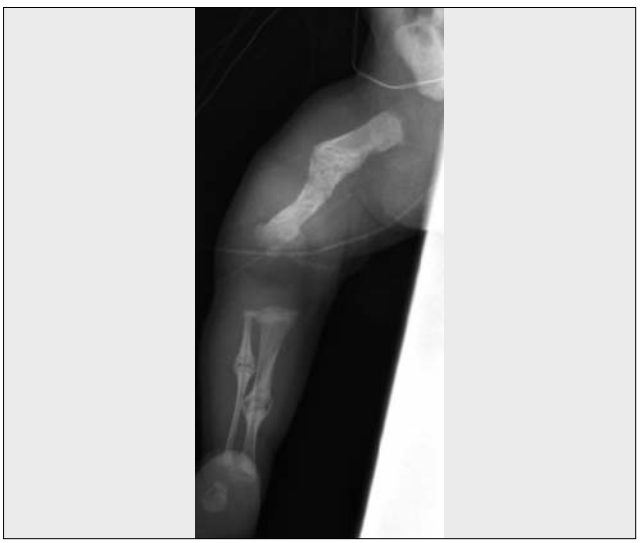

Figure 6. Fractures in Osteogenesis Imperfecta

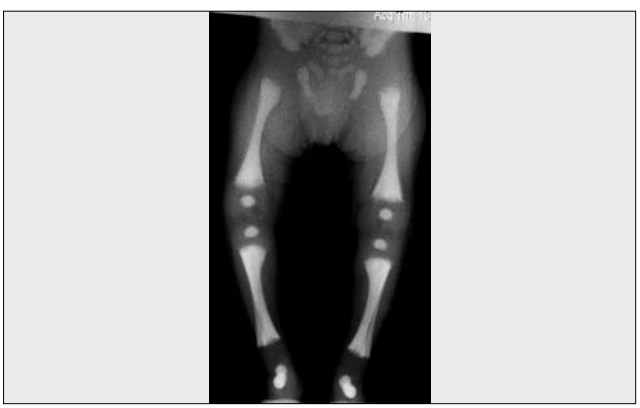

Figure 7. Osteopetrosis, generalized osteosclerosis

dysplasias [SE(M)Ds]. Fractures can be seen in all types of OI (Figure 6), osteosclerotic disorders including osteopetrosis (Figure 7) and severe hypophosphatasia (Figure 8) (7).

Following the evaluation of limb segments and the epiphyseal growth plate, focus on all the skeletal structures available in the genetic skeletal survey is mandatory to recognize a well-described skeletal dysplasia from a previous broad categorization into a specific group. This precise evaluation will include a search for pathognomonic findings, such as snail-shaped iliac bones of Schneckenbecken dysplasia (Figure 9), "lacy" appearance of iliac crest in Dyygve-Melchior-Clausen syndrome (Figure 10), and loss of mandibular angle accompanied by wormian bones and acroosteolysis in pycnodysostosis (Figure 11 a,b,c) (7).

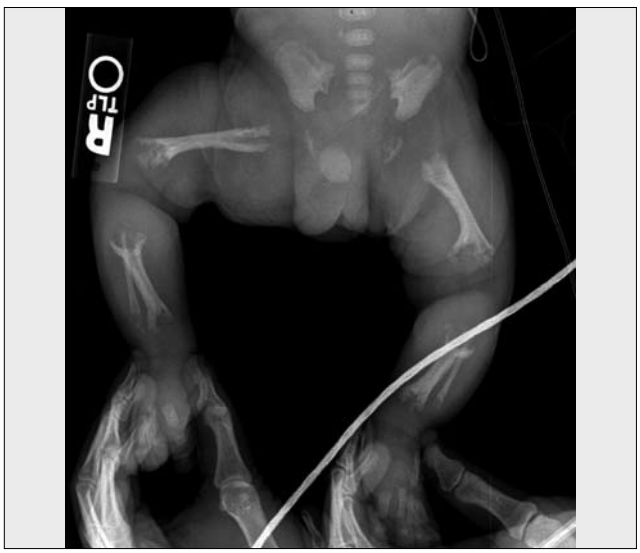

Figure 8. Infantile hypophosphatasia

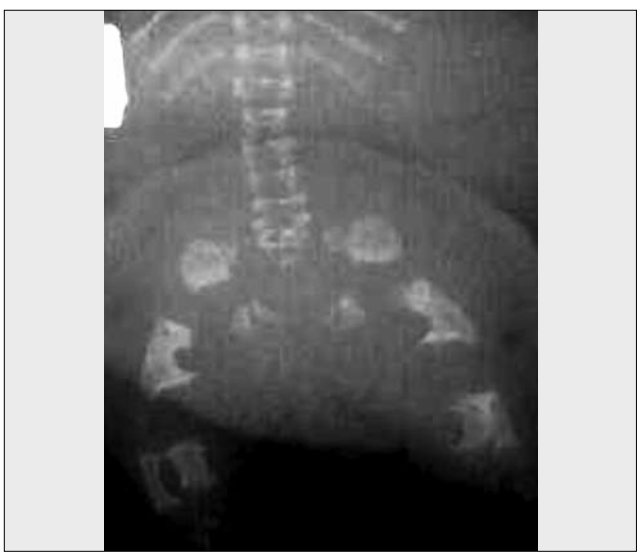

Figure 9. Schneckenbecken dysplasia. Note severe platyspondyly, thin ribs and snail-shaped iliac bones

Step III (Differentiation of Normal Variants from Pathological Abnormalities): This last step requires experience in the field of pediatric radiology. It essentially involves recognition of normal variation from pathological abnormalities in the growing skeleton. Every portion of every bony structure should be looked at in an effort to combine the clinical, often dysmorphic findings previously noted in evaluation of the patient. Pathognomonic findings help to narrow the group of differential diagnosis leading to a specific entity.

At this point, having had a thorough clinical and radiographic assessment, even a simple radiographic grouping can be helpful to the clinician for the establishment of clinical care and follow-up. Table 2 provides a list of the grouping mentioned with common specific entities to consider (7). If a specific diagnosis cannot be made, it is expedient to send the case to a local expert, or an expert group in Skeletal Dysplasias such as the International Skeletal Dysplasia Registry at Cedars Sinai MC [www.csmc.edu/skeletaldysplasia].

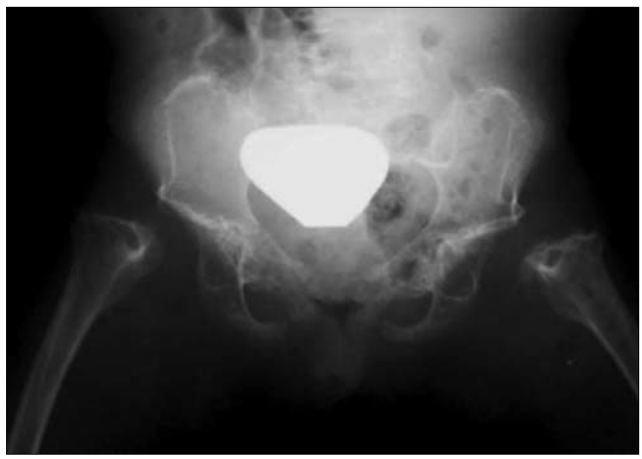

Figure 10. Dyygve-Melchior-Clausen syndrome. Note "lacy" iliac crest

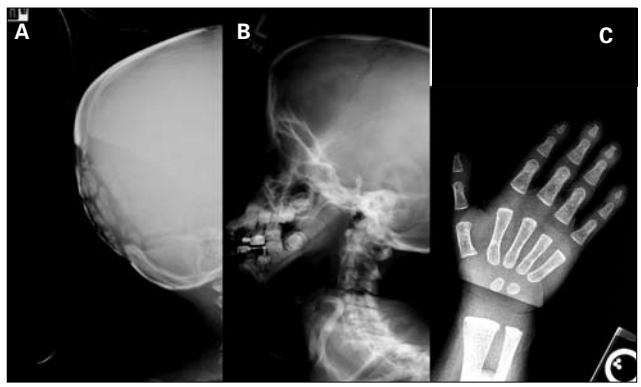

Figure 11. a,b,c. Pycnodysostosis. Loss of mandibular angle with wormian bones, large fontanelle and acroosteolysis in distal phalanges of hand

Table 2. Clues for radiographic diagnosis of skeletal dysplasias

RADIOLOGICAL GROUPS	COMMON ENTITIES	RADIOLOGICAL FINDINGS
Achondroplasia Group		
	Thanatophoric Dysplasia	Skull: Proportionately large skull, narrow skull base, kleeblattschadel Spine: flat, small vertebral bodies with rounded anterior ends Pelvis: small, flared iliac bones; very narrow sacrosciatic notches; flat, dysplastic acetabula Extremities: generalized micomelia: French telephone receiver femurs, round proximal femoral metaphyses with medial spike
	Achondroplasia	Skull: enlarged, midface hypoplasia; rarely hydrocephalus, tight foramen magnum Thorax: small; shortened and anteriorly splayed ribs Spine: slight platyspondyly, short and anteriorly round vertebral bodies that normalize from childhood on; very short pedicles with decreased interpedicular distance marked in lumbar spine; posterior vertebral scalloping that persists through life Pelvis: flared, superiorly and laterally flattened ilia (elephant ear-shaped iliac wings), narrow sacrosciatic notches, flat acetabular roofs Extremities: rhizo-, meso-, and acromelia Hands: brachydactyly, metacarpal metahyseal cupping, phalangeal metaphyseal widening Knees: chevron and upside-down chevron deformity (tibia/femur) Hips: proximal femoral fade-out (infancy); hemispheric capital femoral epiphyses, short femoral necks Legs: proximal and distal fibular overgrowth Arms: prominent deltoid insertion area
	Hypochondroplasia	The radiological findings are identical to achondroplasia but to a milder degree. All cases exhibit interpedicular narrowing in the lumbar spine. There may be brachydactyly, fibular overgrowth, short femoral necks. Other achondroplasia-like changes may or may not be present.
Metatropic Dysplasia Group		
	Metatropic Dysplasia	Thorax: small; short ribs Spine: dense wafer vertebral bodies (newborn), platyspondyly (child, adult), scoliosis (adult) Pelvis and Hips: short, squared iliac wings; flat irregular acetabular roof; narrow sacrosciatic notches; halberd (hunting ax)-shaped proximal femurs Extremities: trumpet-shaped metaphyses (newborn), dumbbell-shaped short tubular bones of hand and feet
Short-Rib Polydactyly Group		
	Short-Rib (With or Without)-Polydactyly Dysplasia	Thorax: small; extremely short horizontal ribs Spine: relatively normal Pelvis: small, dysplastic ilia Extremities: micromelia; round-ended femora; ovoid or tiny normal-shaped tibiae; severe brachydactyly with hypoplastic middle and distal phalanges; polydactyly common, not essential
	Asphyxiating Thoracic Dysplasia (Jeune's syndrome)	Thorax: long and barrel shaped, handlebar clavicles, short horizontal ribs with bulbous anterior ends Spine: normal Pelvis: small; short, flared iiliac wings; trident acetabular roof; narrowed sacrosciatic notches Extremities: generalized shortening, precocious proximal femoral epiphyseal ossification, cone-shaped epiphyses in hand
	Chondroectodermal (Ellis van Creveld) Dysplasia	Thorax: small, moderatley short ribs Pélvis: small; short, flared iliac wings; trident acetabulas; narrowed sacrosciatic nothches Spine: normal Extremities: generalized shortening with meso- and acromelia; premature ossification of capital femoral epiphyses, humeral and femoral bowing Hands: characteristic-postaxial polydactyly, capitate/hamate (and other carpal) fusions, extra carpal boné, cone-shaped epiphyses Feet: polydactyly

Table 2. (continued)

Diastrophic Dysplasia Group		
	Diastrophic Dysplasia	Head: ear pinna calcification Thorax: moderately small Spine: progressive scoliosis, kyphosis, odontoid hypoplasia, cervical kyphosis Extremities: micromelia; short, thck tubular bones; generalized barchydactyly-short ovoid first metacarpal, twisted metatarsal, accessory and irregular carpal bones; epiphyseal dysplasia, joint dislocations
	MED-Multilayered Patellae/Brachydactyly/ Clubfeet	Epiphyseal dysplasia especially at hips (half/quarter moon shaped) Double layered patella (lateral knee radiograph) Mild brachydactyly Clubfeet/ twisted metatarsals
Type II Collagenopathies		
	Spondyloepiphyseal Dysplasia Congenita	Thorax: small; short ribs Spine: oval vertebral bodies (newborn), anteriorly rounded platyspondyly (later) Pelvis: absent pubic ossification (newborn and infancy) Extremities: normally modeled but shortened long bones, significant generalized ossification delay (early) and hypoplastic/dysplastic epiphyses (later), unossified talus/calcaneus in the newborn, normal hands and feet with ossification delay
	Kniest Dysplasia	Thorax: small to normal Spine coronal clefts (newborn/infancy), platyspondyly with end plate irregularity (later) Extremities: dumpbell femurs; generalized ossification delay, epiphyses becoming hypoplastic/dysplastic then megaepiphyses, cloudy effect in the physeal plate (late childhood); hand-bulbous joints (metaphyseal flare/epiphyseal fragmentation)
Other Spondylo-Epi-(Meta) Physeal Dysplasias		
	Spondyloepiphyseal Dysplasia Tarda	Spine: mild platyspondyly with centrally humped end plates with intervertebral disc space narrowing Extremities: mild-moderate "epiphyseal dysplasia" (small and irregular epiphyseal centers), sparing hands and feet
	Dyggve-Melchior-Clausen Syndrome	Skull: microcephaly Thorax: broad; anterior rib widening Spine: double-humped vertebral bodies with end plate notching and posterior scalloping Pelvis: small iliac wings with irregularly calcifies "lacy" iliac crest Extremities: moderate shortening with epi/metaphyseal changes, generalized brachydactyly with cone-shaped epiphyses and small carpal bones
Multiple Epiphyseal Dysplasia and Pseudoachondroplasia Group		
	Multiple Epiphyseal Dysplasia	Spine: young adult-disc herniations into vertebral end plates (Schmorl nodules)Hips: mistakenly diagnosed as bilateral Legg-Calve-Perthes disease or Meyer dysplasia Extremities: small, irregular, flattened ossification centers (epiphyses); small, irregular carpal (and tarsal) centers
	Pseudoachondroplasia	Skull: normal Thorax: mild anterior rib widening Spine: superiorly and inferiorly rounded vertebral bodies, anterior central tongue, normalization of vertebrae (later) Pelvis: rounded iliac wings, hypoplastic, poorly formed acetabular roofs Extremities: mini-epiphyses in the hips, moderate-severe generalized epiphyseal dys plaisa (small, irregular, poorly ossified), metaphyseal widening and irregularity in the knees, proximally rounded metacarpals with mini-epiphyses in the hands, irregular carpal/tarsal bones
Chondrodysplasia Punctata Group		
	Rhizomelic Chondrodysplasia Punctata	Spine: coronal clefting, anteriorly rounded vertebral bodies Extremities: stippling, symmetric bilateral shortening of femurs (and humeri) with less severe shortening of long bones in general

Table 2. (continued)

	Conradi-Hünermann Syndrome/Dysplasia	Spine: diffuse stippling, scoliosis in childhood, abnormal vertebral body formation Extremities: mild symmetric or asymmetric shortening, diffuse generalized stippling in epiphyseal areas; hands and feet-normal aside from stippling **stippling resolves during infancy to develop normal or malformed epiphyseal centers
	Brachytelephalangic Chondrodysplasia Punctata	Spine: hypoplastic vertebral bodies with posterior scalloping and anterior rounding; stippling, especially in the sacrococcygeal area Extremities: normal length (mildly short), brachydactyly with hypoplastic tufts and deformed hypoplastic proximal phalanx of the second digit in the hand and first metatarsal of the foot
Metaphyseal Chondrodysplasia Group		
	Jansen-Type Metaphyseal Chondrodysplasia	Skull: Brachycephaly, platybasia, small mandible Thorax: normal size; expanded irregular anterior rib ends Extremities: extensive irregularity of markedly expanded metaphyses- wide separation of epiphyses from metaphyses
	McKusick-Type Metaphyseal Chondrodysplasia	** Cartilage-Hair Hypoplasia Thorax: anterior rib widening/flaring Spine: slightly small squared vertebral bodies Extremities: flaring cupping fragmentation of metaphyses (especially knees), hips usually sparde; hands-marked shortening with metacarpal and phalangeal cupping and coning
	Schmid-Type Metaphyseal Chondrodysplasia	Thorax: widening anterior rib ends Spine: transient vertebral changes in middle childhood Extremities: metaphyseal flaring, especially at the knees; rounded capital femoral epiphysis with widened growth plate; coax vara; usually no hand involvement
Spondylometaphyseal Dysplasia Group		
	Kozlowski-Type Spondylometaphyseal Dysplasia	Spine: severe platyspondyly, anteriorly rounded/wedged vertebral bodies, increased intervertebral disc spaces, overfaced pedicles Pelvis: short, flared iliac wings; irregular hypoplastic acetabular roof Extremities: widening, sclerosis and irregularity of metaphyses; hemispheric capital femoral epiphysis and widened proximal femoral growth plate with irregularity on both sides; hands-mild shortening with metaphyseal cupping and irregularity , marked carpal ossification delay
Mesomelic Dysplasia Group		
	Dyschondrosteosis	Extremities: symmetrical bowing and shortenng of both radii, shortened ulnae, radiographic Madelung's deformity changes, variable tibial and fibular shortening
Acromelic/Acromesomelic Dysplasia Group		
	Trichorhinophalangeal Syndrome Type I and II	
	Acromesomelic Dysplasia of Maroteaux	Spine:oval vertebral bodies (early), anterior beaking and posterior wedging (later), gibbus and/or kyphoscoliosis ultimately Extremities: shortening of all tubular bones, especially radius/ulna and tibia/fibula; very short tubular bones of hand and feet with cone-shaped epiphyses and large great toes
Dysplasias With Prominent Membranous Bone Involvement		
	Cleidocranial Dysplasia	Skull: large, brachycephalic; wormian bones; wide sutures; persistently open anterior fontanelle Thorax: absence/hypoplasia of clavicles, mildly shortened ribs with downward slope, 11 ribs Spine: significant posterior wedging of thoracic vertebrae Pelvis: high narrow iliac wings, absence/hypoplasia of pubic bones Extremities: numerous pseudoepiphyses of metacarpals and tapered distal phalanges in the hands

Table 2. (continued)

Bent Bone Dysplasia Group		
	Campomelic Dysplasia	Skull: enlarged, narrow with a small face Thorax: mildly short ribs, 11 ribs; severe hypoplasia of the bodies of scapulae Spine: nonossification of thoracic pedicles, cervical kyphosis, hypoplasia of cervical vertebral bodies Pelvis: narrow, tall, iliac wings Extremities: proportionately long, bowed femurs, short tibiae; short long bones of upper extremity
Dysostosis Multiplex Group		
	Dysostosis Multiplex	Skull: enlarged neurocranium, abnormal J-shaped sella Thorax: short, thick clavicles; paddle (oar)-shaped ribs; hypoplastic glenoid Spine: gibbus, superior notched (inferior beaked) thoracolumbar vertebral bodies, upper cervical subluxation Pelvis: flared, small iliac wings with inferior tapering, steep acetabular roofs Extremities: diaphyseal widening of long bones (marrow expansion); dysplastic epiphyses; characteristic hand-brachydactyly, proximal metacarpal "pointing" diaphyseal widening of metacarpals and proximal/middle phalanges, small irregular carpal bones
	Morquio's Syndrome (MPS IVA, B)	Skull: no J-shaped sella Thorax: widened, not oar shaped ribs Spine: middle tonguing, not inferior beaking Pelvis: no tapering of ileum Extremities: proximal metacarpal rounding, not pointing, of hands
	Mucolipidosis II (I Cell Disease)	Extremities: severe osteopenia, poorly defined cortices, "periosteal cloacking" (newborn); rickets-like appearance in distal ulna and radius (infancy) Dysostosis multiplex occurs later
Dysplasias With Decreased Bone Density		
	Osteogenesis imperfecta type II, perinatal lethal	Skull: very poor to no ossification Thorax: small, narrow chest; beaded ribs Spine: severe deossification, collapsed vertebral bodies
	Osteogenesis Imperfecta-other types	Skull: wormian bones (>8 to 10), variable decreased ossification Spine: wedged or collapsed vertebrae Remaining skeleton: osteoporosis and pathological fractures
Dysplasias With Defective Mineralization		
	Hypophosphatasia	Perinatal lethal/Infantile: Skull: decreased ossification with single island-like centers for frontal occipital and parietal bones Thorax: poorly ossified ribs; sporadic dropout of ribs; thin, wavy, fractured ribs Spine: spoardc unossified vertebral bodies, dense and osteopenic vertebrae, butterfly shaped vertebral bodies Extremities: generalized decreased ossification, chromosome-shaped femurs, metaphyseal cupping and irregularity, central luscent defect, bowed femora *clavicles are not affected; infantile form is less severe Adult Generalized osteopenia Extremities: metaphyseal widening (rickets-like chages), punched-out metaphyseal lesions, pathologic fractures
Increased Bone Density Without Modification of Bone Shape Group		
	Osteopetrosis	Generalized increased bone density Skull: thick and dense, especially at the base Thorax: splayed anterior ribs Spine: "sandwich" vertebral bodies Extremities: splayed metaphyses, bone-within-bone configuration, dense metaphyseal bands

Table 2. (continued)

	Pyknodysostosis	Generalized osteosclerosis Skull: marked delay in closure of fontanelles and sutures, wormian bones, obtuse or absent mandibular angle, dense skull Thorax: resorbed acromial ends of clavicles Extremities: resorbed phalangeal tufts
Craniotubular Dysplasias		
	Craniodiaphyseal Dysplasia	Skull: marked thickening and sclerosis of calvarium and facial bones, obliteration of foramina and sinuses Thorax: diffusely widened, sclerotic ribs and clavicles Extremities: straightened, undermodeled long bones diaphyses with metaphyseal sparing; sclerosis (cortical thickening) of the short tubular bones of hands
	Craniometaphyseal Dysplasia	Skull: diffuse hyperostosis of cranialvault base and facial bone, obliterated paranasal sinuses Extremities: sclerosis of diaphyses (early), undermodeled flared metaphyses of long bones (later)
	Pyle Disease	Skull: Mild skull and facial involvement, minimal base-of-skull sclerosis, prominent supraorbital ridging Thorax: mildly thick clavicles and ribs Pelvis: thickened ischium and pubis Extremities: marked undertubulation of long bones, especially distal femurs (Erlenmeyer flask deformity); distal flaring of metacarpals and proximal flaring of phalanges
Disorganized Development of Cartilagenous Bony and Fibrous Components of the Skeleton		
	Spondyloenchondrodysplasia	Spine: severe platyspondyly with end plate irregularity Extremities: enchondromata at distal and proximal ends of long bones, hands and feet are rarely affected
	Dysspondyloenchondromatosis	Spine: vertebral anomalies, hemivertebrae, anisospondyly and end plate irregularity Extremities: typical enchondromata, including hands and feet, with long bone asymmetry
Osteolysis Group		
	Multicentric Carpal/Tarsal Osteolysis With or Without Nephropathy	Extremities (wrist and ankles): deossification of carpal bones, loss of carpal/tarsal contours, bone resorption and collapse, sclerosis sometimes extending into adjascent short tubular bones
Patellar Dysplasia Group		
	Nail-Patella Syndrome	Spine: normal Pelvis: iliac horn in the center of the iliac wing extending posteriorly Extremities: (knees and elbows) hypoplastic or absent patella's, radial head and capitellum hypoplasia/elbow dislocation

Conclusion

The complete group of osteochondrodysplasias, although individually rare, is an important group of disorders for healthcare providers who deal with individuals with short stature. These individuals present with significant morbidities due to destruction of bone and cartilage caused by defects in linear growth, bone modeling and regeneration. Regardless of the specific diagnosis, skeletal dysplasias in general share clinical and radiological findings helping us to group them in several ways. In this review, we aimed to focus on the radiological aspect of assessment of skeletal dysplasias. We also included an outline of the basic clinical approach to an individual with a suspected skeletal dysplasia. The recent advances in the field of molecular pathogenetic mechanisms underlying skeletal dysplasias are beyond the scope of this review. However, we would like to emphasize that accurate clinical, radiological and finally molecular diagnosis of skeletal dysplasias is more important than ever in this era of up-to-date genetic counseling, prenatal, preimplantation genetic diagnoses and hopefully, molecularly targeted therapeutics in the future.

Acknowledgement

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References

1. Orioli IM, Castilla EE, Barbosa-Neto JG. The birth prevalence rates for skeletal dysplasias. J Med Genet 1986;23:328-332.
2. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, Mortier G, Mundlos S, Nishimura G, Rimoin DL, Robertson S, Savarirayan R, Sillence D, Spranger J, Unger S, Zabel B, Superti-Furga. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet 2011;155:943-968.
3. Unger S, Lachman RS, Rimoin DL. Chondrodysplasias. In: Rimoin DL, Connor JM, Pyeritz RE, Korf B (eds) Emery and Rimoin's Principles and Practice of Medical Genetics, 5th ed., vol. 3. Elsevier, Philadelphia, PA, USA, 2007;3709-3753.
4. Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. Am J Med Genet A 2007;143:1-18.
5. Krakow D, Rimoin DL. The skeletal dysplasias. Genet Med 2010;12:327-341.
6. Mortier GR. The diagnosis of skeletal dysplasias: a multidisciplinary approach. Eur J Radiol 2001;40:161-167.
7. Lachman RS. Taybi and Lachman's Radiology of Syndromes, Metabolic Disorders and Skeletal Dysplasias, 5th ed., Elsevier, Philadelphia, PA, USA, 2007.