CHAPTER

16

A Diagnostic Approach to Skeletal Dysplasias

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[AU1]

INTRODUCTION

The skeletal dysplasias are disorders characterized by developmental abnormalities of the skeleton. They form a large heterogeneous group and range in severity from precocious osteoarthropathy to perinatal lethality [1,2]. Disproportionate short stature is the most frequent clinical complication but is not uniformly present. There are more than 100 recognized forms of skeletal dysplasia, which can make determining a specific diagnosis difficult [1]. This process is further complicated by the rarity of the individual conditions. The establishment of a precise diagnosis is important for numerous reasons, including prediction of adult height, accurate recurrence risk, prenatal diagnosis in future pregnancies, and, most important, for proper clinical management. Once a skeletal dysplasia is suspected, clinical and radiographic indicators, along with more specific biochemical and molecular tests, are employed to determine the underlying diagnosis. This process starts with history gathering, including the prenatal and family history. This is followed by clinical examination with measurements and radiographs. It is important to obtain a full skeletal survey because the distribution of affected and unaffected areas is key to making a specific diagnosis [3]. Only after a limited differential diagnosis has been established should confirmatory molecular investigations be considered. When available, histological examination of cartilage is a useful diagnostic tool. This is especially important for those conditions that are lethal in the perinatal period. In these instances, the acquisition of as much information as possible, while the material is available, is critical. This chapter reviews this sequence of diagnostic steps and outlines some of the more important radiographic findings.

[AU2]

BACKGROUND

Each skeletal dysplasia is rare, but collectively the birth incidence is approximately 1/5000 [4,5]. The original classification of skeletal dysplasias was quite simplistic. Patients were categorized as either short trunked (Morquio syndrome) or short limbed (achondroplasia) [6] (Fig. 1). As awareness of these conditions grew, their numbers expanded to more than 200 and this gave rise to an unwieldy and complicated nomenclature [7]. In 1977, N. Butler made the prophetic statement that "in recent years, attempts to classify bone dysplasias have been more prolific than enduring" [8]. The advent of molecular testing allowed the grouping of some dysplasias into families. For example, the type II collagenopathies range from the perinatal lethal form (achondrogenesis type II) to precocious osteoarthritis [9]. Although grouping into molecularly related families has simplified the classification, the number of different genes involved is very large. There remain a large number of dysplasias without a known molecular defect that are grouped with others on the basis of a shared clinical or radiographic feature. The nomenclature continues to undergo revisions as new molecular genetic information becomes available [1]. The nomenclature has been renamed as a nosology to indicate that it represents a catalog of recognized skeletal dysplasias rather than a succinct grouping of the varied and numerous disorders (Table 1). A framework in which to classify the skeletal dysplasias on the basis of

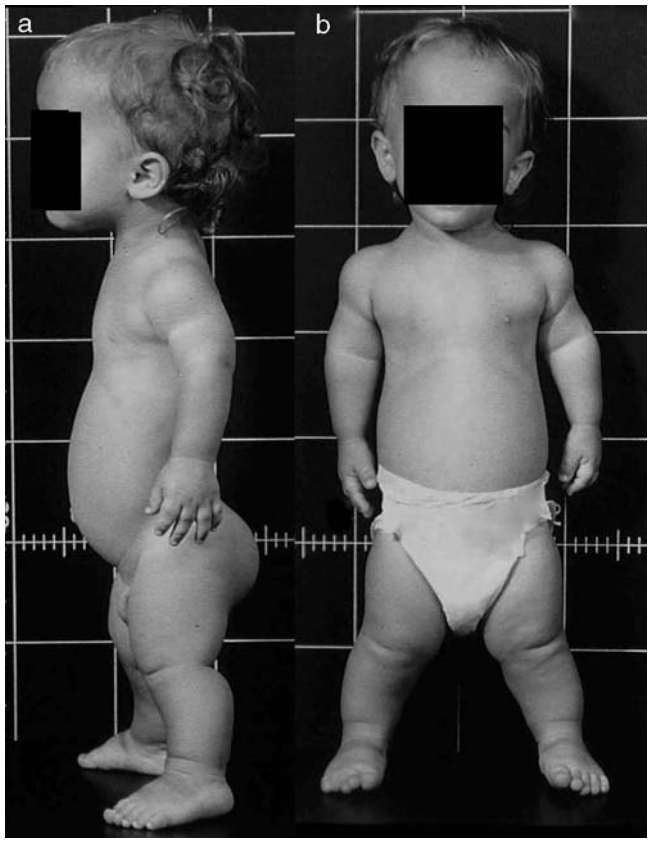


FIGURE 1 Differences in body proportions. (A) A boy with achondroplasia due to the less common FGFR3 mutation (G375C). The shortening is predominantly limb shortening with the proximal segments most affected (rhizomelia). (B) A child with Morquio syndrome (mucopolysaccharidosis type IVA). Although there is overall shortening, it is clear that the trunk is more severely affected.

their molecular defects has recently been developed [10,11] that groups the skeletal dysplasias by the basic function of the defective gene/gene product but does not delineate the biological pathway involved [10].

The spectrum of skeletal dysplasias ranges from perinatal lethal to individuals with normal stature and survival but early onset osteoarthrosis [1]. The approach to diagnosis varies between the lethal/semilethal disorders and those compatible with life; thus, they are reviewed separately. Most lethal skeletal dysplasias (and many nonlethal ones) can be identified on prenatal ultrasound. An attempt should be made to make a precise diagnosis during pregnancy, but this may be impossible until after pregnancy termination/delivery. However, under experienced eyes, a prenatal ultrasound distinction can usually be made between those disorders compatible with life and those lethal prenatally or during early postnatal life. Patients with a nonlethal skeletal dysplasia generally present to their physician for evaluation of short stature. It is sometimes unclear whether the cause of growth failure is systemic or skeletal. Renal, endocrine, and cardiac abnormalities might need to be ruled out. However, these conditions present with proportionate short stature, whereas the dysplasias usually cause disproportionate short stature. Also, some genetic syndromes cause significant prenatal growth failure but should be easily distinguishable on the basis of associated features, such as developmental delay and dysmorphic facies, and by radiographs. In fact, a chapter in *Smith's Recognizable Patterns of Human Malformation* [12] is dedicated to disorders with "very small stature, not skeletal dysplasia."

HISTORY AND PHYSICAL EXAMINATION

When presented with a child with disproportionate short stature, a focused history can give invaluable clues as to the differential diagnosis. In genetics, this starts with prenatal history and includes length at birth. Many of the nonlethal dysplasias (e.g., achondroplasia) present with short stature at birth [13], whereas others (e.g., pseudoachondroplasia) present with a normal birth length with subsequent failure of linear growth [14]. Although the age at which growth failure is first noted for a specific skeletal dysplasia is variable, it tends to be fairly constant and can be used in developing a differential diagnosis. Increasingly, both lethal and nonlethal skeletal dysplasias are being detected on prenatal ultrasound, and it is worthwhile to inquire if any ultrasounds were done during pregnancy and if any discrepancy was noted between fetal size and gestational dates [15].

Inquiry should be made for findings related to the skeletal system. Some of these are obvious, such as joint pain and scoliosis. Some skeletal dysplasias present with multiple congenital joint dislocations (e.g., atelosteogenesis type III) [16]. Other findings that the family might notice include ligamentous laxity or conversely progressive finger contractures. Fetal joint dislocations due to extreme laxity can present at birth as contractures due to failure of proper *in utero* movement [17]. It is also important to ascertain when growth failure was first noted. Sometimes, findings unrelated to the skeletal system can be most helpful in making the diagnosis, such as abnormal hair and susceptibility to infections in cartilage–hair hypoplasia (McKusick metaphyseal dysplasia) [18]. Unfortunately, these findings are by no means constant. Parents may not consider other manifestations relevant to the diagnosis and a history will not be offered unless specifically asked for. Conversely, the diagnosis of a specific skeletal dysplasia may also lead the physician to detect abnormalities that had not been apparent to the patient or the family, such as renal

TABLE 16 International Nosology and Classification of Constitutional Disorders of Bone Osteochondrodysplasias

	Mode of Inheritance	OMIM Syndrome	Comments	Chromosome Locus	Gene	Gene Product
1. Achondroplasia group						
Thanatophoric dysplasia, Type I	AD	187600		4p16.3	FGFR3	FGFR3
(includes San Diego Type)		270230				
Thanatophoric dysplasia, Type II	AD	187601		4p16.3	FGFR3	FGFR3
Achondroplasia	AD	100800		4p16.3	FGFR3	FGFR3
Hypochondroplasia	AD	146000		4p16.3	FGFR3	FGFR3
Hypochondroplasia	AD	146000		other		
SADDAN (severe achondroplasia, developmental delay, acanthosis nigricans)	AD			4p16.3	FGFR3	FGFR3
2. Severe Spondylodysplastic dysplasias						
Lethal platyspondylic skeletal dysplasias	SP	151210				
(Torrance type, Luton type)						
Achondrogenesis type 1A	AR	200600				
Opsismodysplasia	AR	258480				
SMD Sedaghatian Type	AR	250220				
			see also: Thanatophoric dysplasia Types I/II			
			Achondrogenes is Types IB/II and Group 3.			
3. Metatropic dysplasia group						
Fibrochondrogenesis	AR	228520				
Schneckenbecken dysplasia	AR	269250				
Metatropic dysplasia (various forms)	AD	156530				
4. Short-rib dysplasia (SRP) (with or without polydactyly) group						
SRP type I/III	AR	263530				
		263510				
SRP type II	AR	263520				
SRP type IV	AR	269860				
Asphyxiating thoracic dysplasia (Jeune)	AR	208500				
Chondroectodermal Dyplasia (Ellis-van Creveld dysplasia)	AR	225500		4p16	EVC	EVC
Thoracolaryngopelvic dysplasia	AD	187760				

(*continues*)

TABLE 16 (*continued*)

	Mode of Inheritance	OMIM Syndrome	Comments	Chromosome Locus	Gene	Gene Product
5. Atelosteogenesis-Omodysplasia group						
Atelosteogenesis type I (includes "Boomerang dysplasia")	SP	108720				
Omodysplasia I (Maroteaux)	AD	164745				
Omodysplasia II (Borochowitz)	AR	258315				
Atelosteogenesis Type III	AD	108721				
de la Chapelle dysplasia	AR					
6. Diastrophic dysplasia group						
Achondrogenesis 1B	AR	600972		5q32-q33	DTDST	Sul. transporter
Atelosteogenesis type II	AR	256050		5q32- q33	DTDST	Sul. transporter
Diastrophic dysplasia	AR	222600		5q32- q33	DTDST	Sul. transporter
Autosomal Recessive MED	AR	226900	see also: Group 11	5q32-q33	DTDST	Sul. transporter
7. Dyssegmental dysplasia group						
Dyssegmental dysplasia, Silverman-Handmaker type	AR	224410		1p36.1	PLC (HSPG2)	Perlecan
Dyssegmental dysplasia, Rolland-Desbuquois type	AR	224400				
8. Type II collagenopathies						
Achondrogenesis II (Langer- Saldino)	AD	200610		12q13.1-q13.3	COL2A1	Type II collagen
Hypochondrogenesis	AD	200610		12q13.1- q13.3	COL2A1	Type II collagen
Spondyloepiphyseal dysplasia (SED) congenita	AD	183900		12q13.1-q13.3	COL2A1	Type II collagen
Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type	AD	184250		12q13.1-q13.3	COL2A1	Type II collagen
Kniest dysplasia	AD	156550		12q13.1-q13.3	COL2A1	Type II collagen
SED Namaqualand Type	AD			12q13.1-q13.3	COL2A1	Type II collagen
SED with brachydactyly	AD			12q13.1-q13.3	COL2A1	Type II collagen
Mild SED with premature onset arthrosis	AD			12q13.1- q13.3	COL2A1	Type II collagen
Stickler dysplasia Type I	AD	108300		12q13.1- q13.3	COL2A1	Type II collagen
9. Type XI collagenopathies						
Stickler dysplasia Type II	AD	184840	heterogeneous with or without ocular involvement	1p21	COL11A1	Type XI collagen
Marshall syndrome	AD			6p21.3	COL11A2	Type XI collagen
Otospondylomegaepiphyseal dysplasia (OSMED)	AR	215150	Recessive haploinsuficiency mutations	6p21.3	COL11A2	Type XI collagen

Otospondylomegaepiphyseal dysplasia (OSMED)	AD	215150	Dominant mutations; also called Weissenbach-Zweymüller or Stickler dysplasia without ocular involvement	6p21.3	COL11A2	Type XI collagen
10. Other spondyloepi-(meta)-physeal [SE(M)D] dysplasias						
X-linked SED tarda	XLD	313400		Xp22.2-p22.1	SEDT	SEDLIN
SEMD Handigodu Type	AD					
Progressive pseudorheumatoid dysplasia	AR	208230		6q22-q23	WISP3	WNT1-inducible signaling pathway protein 3
Dyggve-Melchior-Clausen dysplasia	AR	223800				
Wolcott-Rallison dysplasia	AR	226980		2p12	EIF2AK3	EIF2AK3
Immuno-osseous dysplasia (Schimke)	AR	242900		2q34-q36	SMARCAL1	SMARCAL1
Schwartz-Jampel syndrome	AR	255800	includes Burton dysplasia and Kyphomelic dysplasia; see also dyssegmental dysplasiaSilverman-Handmaker (see group 7)	1p36.1	PLC (HSPG2)	Perlecan
SEMD with joint laxity (SEMDJL)	AR	271640				
SEMD with dislocations (Hall) (leptodactylic Type)						
Sponastrime dysplasia	AR	271510				
SEMD short limb – abnormal calcification Type	AR	271665	see also: Group 12			
SEMD Pakistani Type	AR	603005		10q23-24	PAPSS2	PAPSS2
			see: opsismodyspl asia Group 2			
11. Multiple epiphyseal dysplasias & pseudoachondroplasia						
Pseudoachondroplasia	AD	177170	see also: Groups 8/10	19p12-13.1	COMP	COMP
Multiple epiphyseal dysplasia (MED)	AD	132400	see also: recessive MED in Group 6	19p13.1	COMP	COMP
(Fairbanks and Ribbing types)	AD	120210		6q13	COL9A1	Type IX collagen
	AD	600204		1p32.2-33	COL9A2	Type IX collagen
	AD	600969		20q13.3	COL9A3	Type IX collagen
	AD	602109		2p23-24	MATN3	matrilin 3
Familial hip dysplasia (Beuke)	AD	142669		4q35		

(*continues*)

TABLE 16 (*continued*)

	Mode of Inheritance	OMIM Syndrome	Comments	Chromosome Locus	Gene	Gene Product
12. Chondrodysplasia punctata (CDP) (stippled epiphyses group)						
Rhizomelic CDP Type 1	AR	215100		6q22-q24	PEX7	PTS2 peroxisomal biogenesis receptor
Rhizomelic CDP Type 2	AR	222765		1q42	DHPAT	DHAPAT
Rhizomelic CDP Type 3	AR	600121		2q31	AGPS	ADHAPS
Zellweger syndrome	AR	214100		7q11.23	PEX1	Peroxin-1
	AR	214100		8q21.1	PEX2	Peroxin-2
	AR	214100		6q23	PEX3	Peroxin-3
	AR	214100		12p13.3	PEX5 (PXR1)	Peroxin-5
	AR	214100		6p21.1	PEX6	Peroxin-6
	AR	214100		17q11.2	PEX12	Peroxin-12
CDP Conradi-Hünermann Type	XLD	300205		Xp11	EBP	EBP
CDP X-linked recessive Type	XLR	302950		Xp22.3	ARSE	Arylsulfatase E
(brachytelephalangic)		302940				
CDP Tibia-metacarpal Type	AD	118651				
CHILD (limb reduction icthyosis)	XLD	308050		Xp11	EBP	EBP
CHILD (limb reduction icthyosis)	XLD	308050		Xq28	NSDHL	NAD(P)H steroid dehydrogenase like protein
Hydrops-ectopic calcification-motheaten appearance HEM (Greenberg dysplasia)	AR	215140				
Dappled diaphyseal dysplasia	AR					
13. Metaphyseal dysplasias						
Jansen Type	AD	156400		3p22-p21.1	PTHR1	PTHR/PTHRP
Schmid Type	AD	156500		6q21-q22.3	COL10A1	Type X collagen
Cartilage-Hair-Hypoplasia (McKusick)	AR	250250		9p21-p12	RMRP	RNA subunit of RMRP RNA'ase
Metaphyseal dysplasia without hypotrichosis	AR	250460		9p21-p12	RMRP	RNA subunit of RMRP RNA'ase
Metaphyseal anadysplasia (various types)	AD/ XLD	309645				
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman Diamond)	AR	260400		7p11-q11		
Adenosine deaminase (ADA) deficiency	AR	102700		20q- 13.11	ADA	Adenosine deaminase
Metaphyseal chondrodysplasia Spahr Type	AR	250400				
Acroscyphodysplasia (various types)	AR	250215				

14. Spondylometaphyseal dysplasias (SMD)						
Spondylometaphyseal dysplasia Kozlowski Type	AD	184252				
Spondylometaphyseal dysplasia (Sutcliffe/corner fracture Type)	AD	184255				
SMD with severe genu valgum (includes Schmidt and Algerian Types)	AD	184253				
			see also: SMD Sedaghatian Type (Group 2)			
15. Brachyolmia spondylodysplasias						
Hobaek (includes Toledo Type)	AR	271530-630				
Maroteaux type	AR					
Autosomal dominant type	AD	113500				
16. Mesomelic dysplasias						
Dychondrosteosis (Leri-Weill)	Pseudo AD	127300		Xpter- p22.32	SHOX	Short stature homeobox protein
Langer type (homozygous dyschondrosteosis)	Pseudo AR	249700	Homozygous dominant	Xpter-p22.32	SHOX	Short stature homeobox protein
Nievergelt Type	AD	163400				
Kozlowski-Reardon Type	AR					
Reinhardt-Pfeiffer Type	AD	191400				
Werner Type	AD	188770				
Robinow Type, dominant	AD	180700				
Robinow Type, recessive	AR	268310		9q22	ROR2	Receptor tyrosine kinase-like orphan receptor 2
Mesomelic dysplasia with synostoses	AD	600383				
Mesomelic dysplasia Kantaputra Type	AD	156232		2q24- q32		
Mesomelic dysplasia Verloes Type	AD	600383				
Mesomelic dysplasia Savarirayan Type						
17. Acromelic dysplasias						
Acromicric dysplasia	AD	102370				
Geleophysic dysplasia	AR	231050				
Myhre dysplasia		139210				
Weill-Marchesani dysplasia	AR	277600				
Trichorhinophalangeal dysplasia Types I/III	AD	190350190351		8q24.12	TRPS1	
Trichorhinophalangeal dysplasia Type II (Langer-Giedion)	AD	150230		8q24.11-q24.13	TRPS1 EXT1 (contiguous gene deletion)	

(*continues*)

TABLE 16 (*continued*)

	Mode of Inheritance	OMIM Syndrome	Comments	Chromosome Locus	Gene	Gene Product
Brachydactyly type A1	AD	112500		2q35		
Brachydactyly type A2	AD	112600				
Brachydactyly type A3		112700				
Brachydactyly type B	AD	113000		9q22	ROR2	Receptor tyrosine kinase-like orphan receptor 2
Brachydactyly type C	AD	113100		20q11	CDMP1	cartilage derived morphogenic protein 1
	AD			12q24		
Brachydactyly type D	AD	113200				
Brachydactyly type E	AD	113000				
Pseudohypoparathyroidism (Albright Hereditary Osteodystrophy)	AD	103580		20q13	GNAS1	guanine nucleotide binding protein of adenylate
Acrodysostosis	SP(AD)	101800				
Saldino-Mainzer dysplasia	AR	266920				
Brachydactyly-hypertension dysplasia (Bilginturan)	AD	112410		12p12.2-p11.2	HTNB	
Craniofacial conodysplasia	AD					
Angel-shaped phalango-epiphyseal dysplasia (ASPED)	AD	105835				
Camptodactyly arthropathy coxa vara pericarditis (CACP)	AR	208250		1q25-31	PRG4	Proteoglycan-4
18. Acromesomelic dysplasias						
Acromesomelic dysplasia Type Maroteaux	AR	201250		9p13-p12		
Acromesomelic dysplasia Type Campailla-Martinelli	AR					
Acromesomelic dysplasia Type Ferraz/Ohba	AD					
Acromesomelic dysplasia Type Osebold Remondini	AD	112910				
Grebe dysplasia	AR	200700		20q11.2	CDMP1	cartilage derived morphogenic protein 1
Cranioectodermal dysplasia	AR	218330				
19. Dysplasias with predominant membranous bone involvement						
Cleidocranial dysplasia	AD	119600		6p21	CBFA1/RUNX-2	core binding factor α1-subunit
Yunis-Varon dysplasia	AR	216340				
Parietal foramina (isolated)	AD	168500		11p11.2	ALX4	Aristaless-like 4
Parietal foramina (isolated)	AD	168500		5q34- q35	MSX2	Muscle segment homeobox 2

20. Bent-bone dysplasia group						
Campomelic dysplasia	AD	114290		17q24.3-q25.1	SOX9	SOX9
Cumming syndrome	AR	211890				
Stüve-Wiedemann dysplasia	AR	601559				
			see also Antley-Bixler syndrome			
21. Multiple dislocations with dysplasias						
Larsen syndrome	AD	150250		3p21.1-p14.1		
Larsen-like syndromes (including La Reunion Island)	AR	245600				
Desbuquois dysplasia	AR	251450				
Pseudodiastrophic dysplasia	AR	264180				
			see also: Group 10			
22. Dysostosis multiplex group						
Mucopolysaccharidosis IH	AR	252800		4p16.3	IDA	α-1-Iduronidase
Mucopolysaccharidosis IS	AR	252800		4p16.3	IDA	α-1-Iduronidase
Mucopolysaccharidosis II	XLR	309900		Xq27.3-q28	IDS	Iduronate-2-sulfatase
Mucopolysaccharidosis IIIA	AR	252900		17q25.3	HSS	Heparan sulfate sulfatase
Mucopolysaccharidosis IIIB	AR	252920		17q21		N-Ac-α-D-glucosaminidase
Mucopolysaccharidosis IIIC	AR	252930				Ac-Coa:α-glucosamine-N-acetyltransferase
Mucopolysaccharidosis IIID	AR	252940		12q14	GNS	N-Ac-glucosamine-6-sulfatase
Mucopolysaccharidosis IVA	AR	253000		16q24.3	GALNS	Galactosamine-6-sulfatase
Mucopolysaccharidosis IVB	AR	230500	See also: GM1-Gangliosidosis	3p21.33	GLBI	β-Galactosidase
Mucopolysaccharidosis VI	AR	253200		5q13.3	ARSB	Arylsulfatase B
Mucopolysaccharidosis VII	AR	253220		7q21.11	GUSB	β-Glucuronidase
Fucosidosis	AR	230000		1p34	FUCA	α-Fucosidase
a-Mannosidosis	AR	248500		19p13.2-q12	MAN	α-Mannosidase
b-Mannosidosis	AR	248510		4q22-q25	MANB	β-Mannosidase
Aspartylglucosaminuria	AR	208400		4q32-q33	AgA	Aspartylglucosaminidase
GM1 Gangliosidosis, several forms	AR	230500	See also: MPS IV B	3p21.33	GLB1	β-Galactosidase
Sialidosis, several forms	AR	256550		6p21.3	NEU	α-Neuraminidase
Sialic acid storage disease	AR	269920		6q14-q15	SIASD	
Galactosialidosis, several forms	AR	256540		20q13.1	PPGB	β-Galactosidase protective protein
Multiple sulfatase deficiency	AR	272200				Multiple sulfatases

(*continues*)

TABLE 16 (*continued*)

	Mode of Inheritance	OMIM Syndrome	Comments	Chromosome Locus	Gene	Gene Product
Mucolipidosis II	AR	252500		4q21-23	GNPTA	N-Ac-Glucosamine-phosphotransferase
Mucolipidosis III	AR	252600	see also: Groups 8,10,11,14	4q21-23	GNPTA	N-Ac-Glucosamine-phosphotansferase
23. Osteodysplastic slender bone group						
Type I microcephalic osteodysplastic dysplasia	AR	210710				
Type II microcephalic osteodysplastic dysplasia	AR	210720				
Microcephalic osteodysplastic dysplasia (Saul Wilson).	AR	210730				
24. Dysplasias with decreased bone density						
Osteogenesis imperfecta I (normal teeth)	AD	166200		17q21-q22	COL1A1	Type I collagen
Osteogenesis Imperfecta I (normal teeth)		166200		7q22.1	COL1A2	Type I collagen
Osteogenesis imperfecta I (opalescent teeth)	AD	166240		7q22.1	COL1A2	Type I collagen
	AD	166240		7q22.1	COL1A2	Type I collagen
Osteogenesis imperfecta II	AD	166210		17q21-q22	COL1A1	Type I collagen
	AD	166210		7q22.1	COL1A2	Type I collagen
	AD	259400		17q21-q22	COL1A1	Type I collagen
Osteogenesis imperfecta III	AD	259420		17q21-q22	COL1A1	Type I collagen
	AD	259420		7q22.1	COL1A2	Type I collagen
	AR	259420		7q22.1	COL1A2	Type I collagen
	AR	259420				
Osteogenesis imperfectaIV (normal teeth)	AD	166220		7q22.1	COL1A2	Type I collagen
	AD	166220		17q	COL1A1	Type I collagen
Osteogenesis imperfecta IV (opalescent teeth)	AD	166220		7q22.1	COL1A2	Type I collagen
	AD	166220		17q21-q22	COL1A1	Type I collagen
Osteogenesis Imperfecta V						
Osteogenesis Imperfecta VI						
Cole-Carpenter dysplasia	SP	112240				
Bruck dysplasia I	AR	259450		17p12		
Bruck dysplasia II						
Singleton-Merton dysplasia	AR					
Osteopenia with radiolucent lesions of the mandible	AD	166260				
Osteoporosis-pseudoglioma dysplasia	AR	259770		11q12-q13	LRP5	Low density lipoprotein receptor-related protein:

Geroderma osteodysplasticum	AR	231070				
Idiopathic juvenile osteroporosis	SP	259750				
25. Dysplasias with defective mineralization						
Hypophosphatasia-perinatal lethal and infantile forms	AR	241500		1p36.1-p34	ALPL	alkaline phosphatase
Hypophosphatasia adult form	AD	146300		1p36.1-p34	ALPL	alkaline phosphatase
Hypophosphatemic rickets	XLD	307800		Xp22.2-p22.1	PHEX	Phosphate regulating endopeptidase
	AD	193100		12p13.3	FGF23	Fibroblast growth factor 23
Neonatal hyperparathyroidism	AR	239200		3q21- q24	CASR	Calcium-sensing receptor
Transient neonatal hyperparathyrodism with hypocalciuric hypercalcemia	AD	145980	Some families not linked to this locus	3q21-q24	CASR	Calcium-sensing receptor
26. Increased bone density without modification of bone shape						
Osteopetrosis						
Infantile form	AR	259700		11q13.4- q13.5	TC1RG1	vacuolar proton pump
	AR			16p13	CLCN7	Chloride channel 7
With infantile neuroaxonal dysplasia	AR?	600329				
Delayed forms	AD	166600				
Intermediate form (possibly heterogeneous)	AR	259710				
With renal tubular acidosis (carbonic anhydrase II deficiency)	AR	259730		8q22	CA2	carbonic anhydrase II
Dysosteosclerosis	AR	224300				
With ectodermal dysplasia and immune defect (OLEDAID)	XL	300301		Xq28	IKBKG (NEMO)	NF-kB signalling
Osteomesopyknosis	AD	166450				
Cranial osteosclerosis with bamboo hair (Netherton)	AR	256500				
Pyknodysostosis	AR	265800		1q21	CTSK	cathepsin K
Osteosclerosis Stanescu type	AD	122900				
Osteopathia striata (isolated)	SP					
Osteopathia striata with cranial sclerosis	AD/XL D?	166500				
	D?					
Melorheostosis	SP	155950				
Osteopoikilosis	AD	166700				
Mixed sclerosing bone dysplasia	SP					

(*continues*)

TABLE 16 (*continued*)

	Mode of Inheritance	OMIM Syndrome	Comments	Chromosome Locus	Gene	Gene Product
27. Increased bone density with diaphyseal involvement						
Diaphyseal dysplasia Camurati Engelmann	AD	131300		19q13.1-13.3	TGFb1	transforming growth factor beta 1
Diaphyseal dysplasia with anemia (Ghosal)	AR	231095				
Craniodiaphyseal dysplasia	?AR	218300 122860				
Lenz Majewski dysplasia		151050				
Endosteal hyperostosis						
van Buchem type	AR	239100		17q11.2	SOST	Sclerostin
Sclerosteosis	AR	269500		17q11.2	SOST	Sclerostin
Worth type	AD	144750				
Sclero-osteo-cerebellar dysplasia	AR	213002				
Kenny Caffey dysplasia Type I	AR	244460		1q41-q42		
Kenny Caffey dysplasia Type II	AD	127000				
Osteoectasia with hyperphosphatasia (Juvenile Paget disease)	AR	239000				
Diaphyseal medullary stenosis with bone malignancy	AD	112250		9p21-p22		
Oculodentoosseous dysplasia	AR	257850				
	AD	164200		6q22-24		
Trichodentoosseous dysplasia	AD	190320		17q21	DLX3	Distal-less 3 protein
28. Increased bone density with metaphyseal involvement						
Pyle dysplasia	AR	265900				
Craniometaphyseal dysplasia						
Severe type	AR	218400				
Mild type	AD	123000		5p15.2- p14.2	ANKH	Pyrophosphate channel
			see also: Group 29			
29. Craniotubular digital dysplasias						
Frontometaphyseal dysplasia	XLR	305620				
Osteodysplasty, Melnick-Needles	XLD	309350				
Precocious osteodysplasty (terHaar dysplasia)	AR	249420				
Otopalatodigital syndrome Type I	XLD	311300		Xq28		
Otopalatodigital syndrome Type II	XLR	304120				
			see also: Group 28			

30. Neonatal severe osteosclerotic dysplasias						
Blomstrand dysplasia	AR	215045		3p22-p21.1	PTHR1	PTH/PTH-RP
Raine dysplasia	AR	259775				
Prenatal onset Caffey disease	AD ?AR	114000	see also: Mucolipidosis II			
Astley-Kendall dysplasia	AR					
31. Disorganized development of cartilaginous and fibrous components of the skeleton						
Dysplasia epiphysealis hemimelica	SP	127800				
Multiple cartilaginous exostoses	AD	133700		8q23-q24.1	EXT1	exostosin-1
	AD	133701		11p12-p11	EXT2	exostosin-2
	AD	600209		19p		
Enchondromatosis, Ollier	SP	166000				
Enchondromatosis with hemangiomata (Maffucci)	SP	166000				
Spondyloenchondromatosis	AR	271550				
Spondyloenchondromatosis with basal ganglia calcification	AR					
Dysspondyloenchondromatosis						
Metachondromatosis	AD	156250				
Osteoglophonic dysplasia	AD	166250				
Enchondromatosis	AD	166000				
Carpotarsal osteochondromatosis	AD	127820				
Fibrous dysplasia (McCune-Albright and others)	SP mosaic	174800		20q13	GNAS1	guanine nucleotide-binding protein, α subunit
Jaffe Campanacci	SP					
Fibrodysplasia ossificans progressiva	AD	135100		4q27- 31		
Cherubism	AD	118400		4p16.3	SH3BP2	SH3 domain-binding protein 2
Cherubism with gingival fibromatosis	AR	135300				
32. Osteolyses						
Multicentric-hands and feet						
Multicentric carpal-tarsal osteolysis with and without nephropathy	AD	166300				
Shinohara carpal-tarsal osteolysis						
Winchester syndrome	AR	277950				
Torg syndrome	AR	259600		16q12-21	MMP2	MMP2

(*continues*)

TABLE 16 (*continued*)

	Mode of Inheritance	OMIM Syndrome	Comments	Chromosome Locus	Gene	Gene Product
Distal phalanges						
Hadju-Cheney syndrome	AD	102500				
Mandibuloacral syndrome	AR	248370				
Diaphyses and metaphyses						
Familial expansile osteolysis	AD	174810		18q21.1- q22	TNFRSF11A	RANK
Juvenile hyaline fibromatosis (includes systemic juvenile hyalinosis)	AD	228600				
33. Patella dysplasias						
Nail patella dysplasia	AD	161200		9q34.1	LMX1B	LIM homeobox transcription factor 1
Scypho-patellar dysplasia	AD					
Ischiopubic patellar dysplasia	AD	147891				
Genitopatellar syndrome						
Ear patella short stature syndrome (Meier Gorlin)	AR	224690				

abnormalities in asphyxiating thoracic dysplasia (ATD or Jeune syndrome) [19]. Most skeletal dysplasias are associated with normal intellectual development. However, a developmental history should be taken because there are notable exceptions to this rule. For children with achondroplasia, there is a gross motor developmental delay in the first 2 years of life likely related to large head size and ligamentous laxity [20]. Specific learning disabilities have been reported in hypochondroplasia and achondroplasia, but their significance remains controversial [21]. Certainly, there is marked developmental delay in children with the syndrome known as severe achondroplasia with developmental delay, which is a related fibroblast growth factor receptor 3 disorder [22,23]. Dgyvve–Melchior–Clausen and dysteosclerosis are both rare dysplasias associated with severe to profound mental retardation [24,25].

A detailed family history should also be taken. Obviously, if another family member has a skeletal dysplasia, this will be important in assessing the mode of inheritance. It is also important to note parental heights since it is possible that the child might simply have familial short stature. Frequently, there is no family history of dwarfism because many, if not most, of the skeletal dysplasias, including the most common (achondroplasia), are autosomal dominant but most often caused by new mutations rather than being inherited [26]. Certain dysplasias are more common among certain ethnic groups, such as cartilage–hair hypoplasia in the Amish [27] and spondyloepimetaphyseal dysplasia with joint laxity in the South African Afrikaner population [28].

On physical examination, various growth parameters must be precisely determined. It is important to note not only the height of the child but also the weight and head circumference. This can sometimes establish a pattern; for example, in children with achondroplasia, the head circumference is larger than normal but height is dramatically reduced compared to normal [13]. A simple method of determining proportions consists of measuring the lower segment (symphysis pubis to floor) and subtracting this figure from the total height to determine the upper segment and then calculating the upper segment-to-lower segment ratio. This ratio, along with the arm span-to-height ratio, is used to document whether the spine or limbs are more severely shortened. When there is limb shortening, it is helpful to classify it as rhizomelic (proximal), mesomelic (middle), or acromelic (distal) depending on which segment is most affected. Once a specific diagnosis has been established, it is useful to plot the child's growth against disorder-specific growth curves. Specialized growth curves have been developed for achondroplasia, pseudoachondroplasia, spondyloepiphyseal dysplasia congenita, and diastrophic dysplasia [13,29]. These curves are most helpful for achondroplasia and should be used more cautiously for the other disorders because they show much more allelic heterogeneity and thus much greater phenotypic variability. In addition, assessment of symmetry or asymmetry can indicate certain diagnoses (e.g., chondrodysplasia punctata Conradi–Hunermann) [30] (Fig. 2).

As in other genetic syndromes, ancillary signs can be helpful in securing the diagnosis; thus, a general physical examination is also recommended. These signs include such findings as congenital heart disease, polydactyly, and dystrophic nails in chondroectodermal dysplasia (Ellis–van Creveld syndrome) [31]. A single finding is never present in 100% of patients but if present can be instructive. A good example of this is the cystic ear

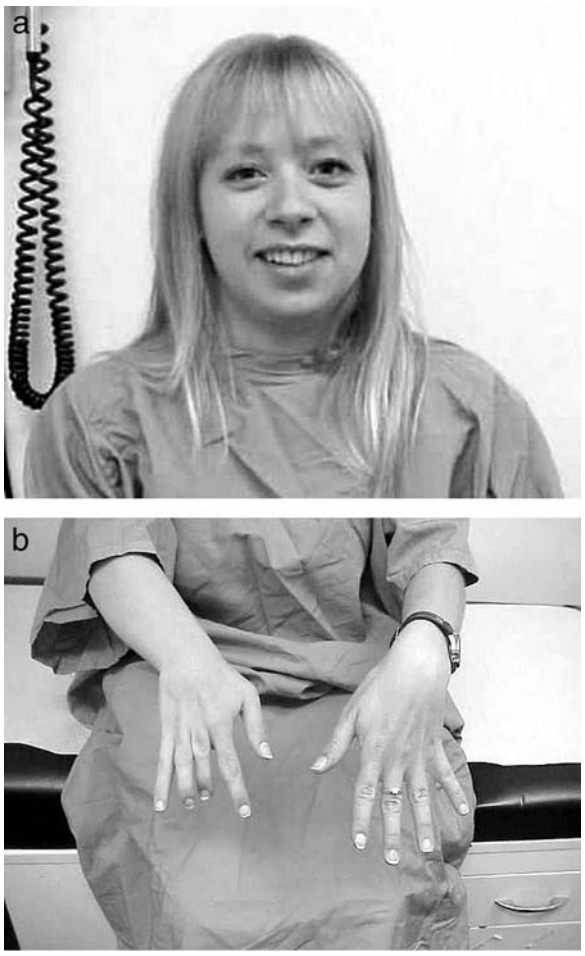


FIGURE 2 (A) A 21-year-old woman with chondrodysplasia punctata Conradi–Hunerman type CDP-CH. Her face and limbs show the asymmetry characteristic of this disorder. She presented at birth with hypoplasia of the right side of her body and icthyosis. She also had scoliosis, bilateral club feet, and laryngeal stenosis requiring surgical correction. On radiographs, there were multiple areas of stippling, particularly at the right knee and ankle. Her diagnosis was confirmed by plasma sterol analysis, which showed an increase in 8(9) cholestenol (analysis by Dr. Lisa Kratz and Dr. Richard Kelley).

[AU6] [AU5] [AU15]

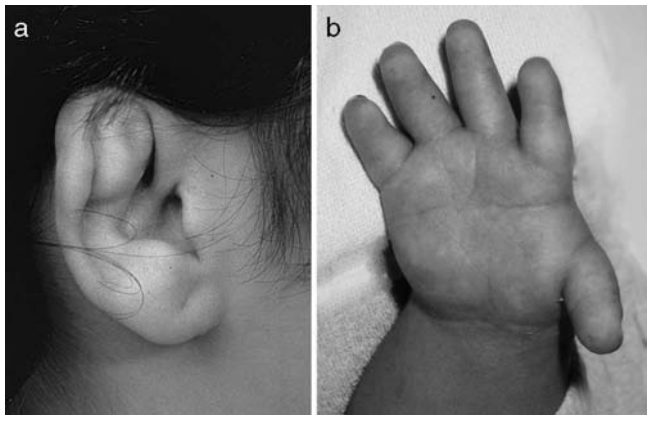


FIGURE 3 (A) A young child with diastrophic dysplasia. Note the gross deformation of the helical contour of the ear by the underlying cystic swelling. Generally, these swellings are not present at birth but develop during the first year of life and can be quite useful in establishing the diagnosis. (B) Another clue to the diagnosis of diastrophic dysplasia is this deformity of the thumb, termed the hitchhiker thumb, caused by a shortened first metacarpal.

swellings seen in children with diastrophic dysplasia, which are fairly specific for this disorder [32] (Fig. 3). In general, children with skeletal dysplasias do not show dysmorphic features of the head and neck, but one important feature is the Pierre–Robin sequence seen in the type II collagenopathies and campomelic dysplasia [9] (Fig. 4).

DIAGNOSTIC IMAGING

The number of clinical discriminators is far less than the number of skeletal dysplasias; thus, radiographs are necessary for diagnosis. A complete skeletal survey is recommended because the demonstration of normal findings in a specific region (e.g., the hands) can be important in making a differential diagnosis. The genetic skeletal survey should include the following views: lateral skull, anteroposterior and lateral thoracic and lumbar spine, and separate lateral views of the cervical spine, thorax, pelvis with hips, long bones, hands, and feet [3]. An assessment of the size, structure, and shape of the individual bones should also be performed. The dysplasias are traditionally classified by the parts of the skeleton that are involved. The patterns may include any or all of the following: spondylo-, epiphyseal-, metaphyseal-, and diaphyseal abnormalities. Recognition of the area or areas involved helps to narrow the differential. Pseudoachondroplasia (PSACH) is a classic example of a spondyloepimetaphyseal dysplasia. In childhood, children with PSACH have anterior beaking of their lumbar vertebrae, small irregular epiphyses, and metaphyseal flaring (Fig. 5). This pattern of features is specific to PSACH and sufficient for making the diagnosis [33]. This dysplasia also illustrates that radiographic features of a dysplasia are not static. As with most dysplasias, the diagnosis of PSACH is much more difficult using adult radiographs when the epiphyses have fused and the anterior beaking of the vertebrae is replaced by nonspecific platyspondyly.

In addition to the pattern of skeletal abnormalities, the region of the skeleton that is affected can be used to narrow the differential diagnosis. For example, in cartilage–hair hypoplasia (CHH) (McKusick metaphyseal dysplasia), the metaphyses are abnormal with relative sparing of the epiphyses and spine, but not all metaphyses are equally affected. The knees are most compromised, with relative sparing of hips [34]. This pattern of affected regions helps to differentiate CHH from the

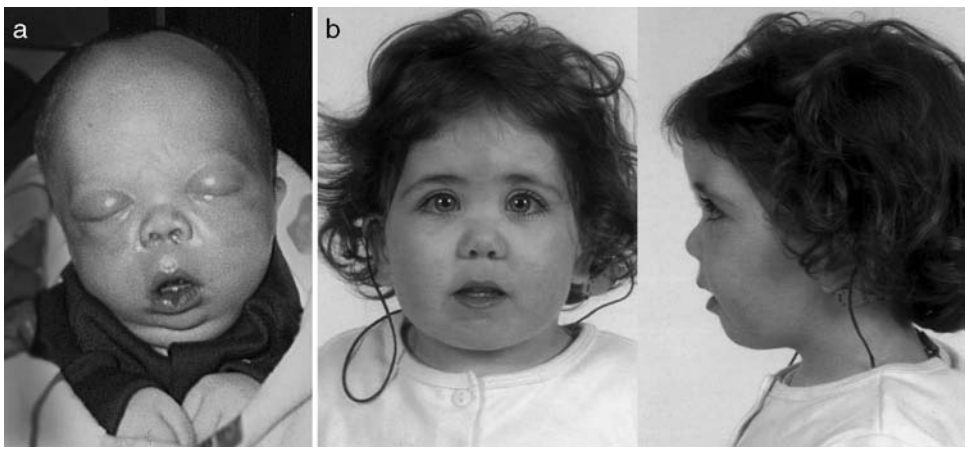


FIGURE 4 (A) A newborn with campomelic dysplasia and typical craniofacial features. He has midface hypoplasia, protuberant eyes, and Pierre–Robin sequence (U-shaped cleft soft palate and micrognathia. (B) A 4-year-old girl with Stickler syndrome. She has high myopia and hearing loss (note hearing aids), in addition to the Pierre–Robin sequence. She has a proven type II collagenopathy with a 9 base pair deletion in exon 41.

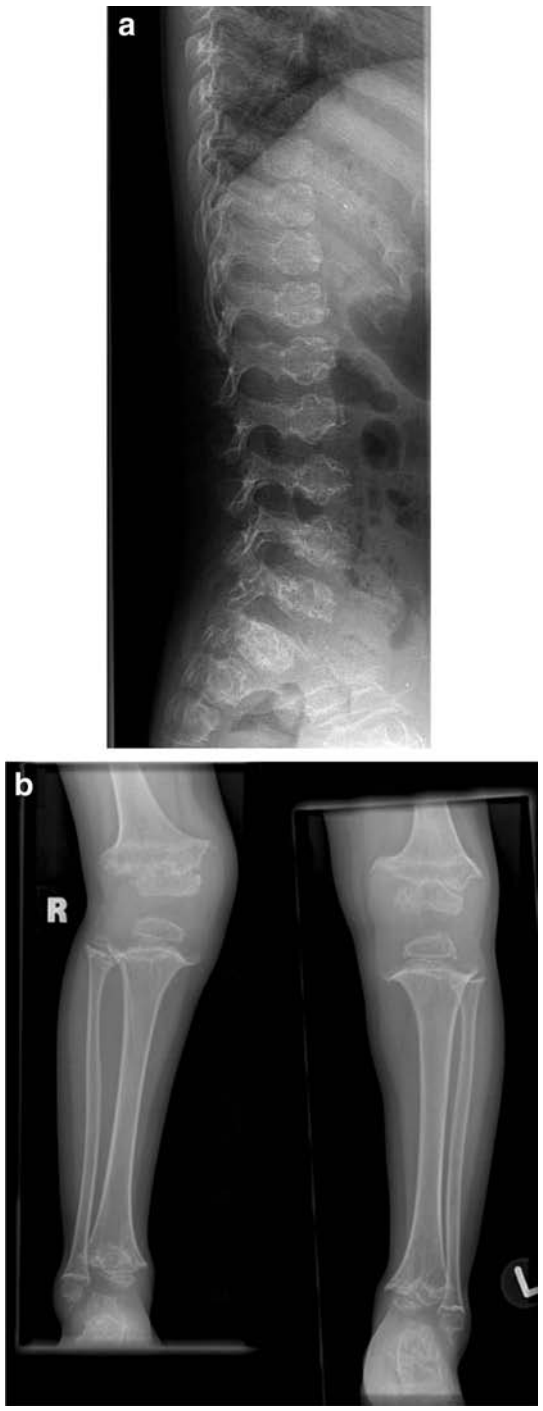


FIGURE 5 Radiographs of a 5-year-old girl with pseudoachondroplasia (PSACH). The lateral spine radiograph shows anterior beaking with central protrusion, which is typical of the disorder. At her knee, the epiphyses are small and dysplastic and the metaphyses are flared. In PSACH, the radiographic findings are sufficient and specific enough to allow for diagnosis.

other metaphyseal dysplasias and nutritional rickets [35]. The pattern is key to the diagnosis because few radiographic features are specific. One notable exception is the finding of iliac horns (Fig. 6) in nail–patella syndrome, which are essentially pathognomonic for the disorder [36].

Although it is a subjective assessment, the bone quality can also help to discriminate between various dysplasias. Dense bones are seen in several disorders, including osteopetrosis and pycnodysostosis [37,38] (Fig. 7). Osteopenia is seen in another group of disorders, including osteogenesis imperfecta and hypophosphatasia [39]. Bone mineral density studies are available to quantify the impression of osteopenia, but care should be taken to use age-matched controls.

The spine radiographs can reveal more than simple platyspondyly. In the newborn period, several disorders, including Kniest dysplasia and various forms of chondrodysplasia punctata, have multiple coronal clefts [40]. One of the more specific findings in the spine is the "double hump" seen in Dgyvve–Melchior–Clausen syndrome [24] (Fig. 8). Again, it is important to keep in mind the "fourth dimension" or the evolution of findings over time [41]. The humped vertebrae of spondyloepiphyseal dysplasia tarda will not be apparent until adolescence, and the abnormalities in the lumbar spine in sponastrime dysplasia change from platyspondyly with an anterior protrusion to biconcave deformities of the posterior portion of the vertebral bodies [42,43].

Abnormal findings have been recorded for every bone or anatomical region. The hands are worthy of special mention because of the variety of abnormal findings and their frequently critical role in establishing a diagnosis. Although bone age is not reliable for estimating potential adult height in a person with a skeletal dysplasia, it can be a useful indicator. Several skeletal dysplasias show retarded osseous maturation, whereas advanced carpal

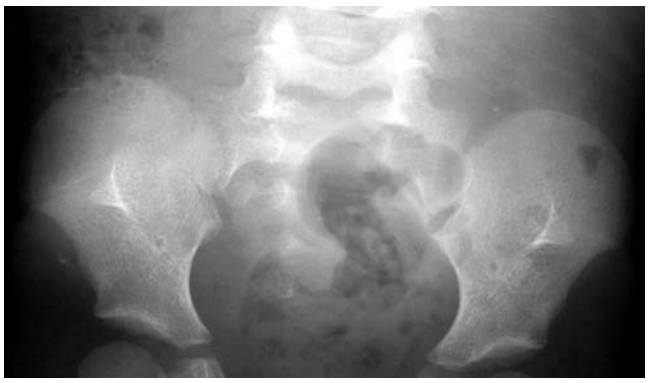


FIGURE 6 Radiograph of the pelvis of an approximately 4-year-old girl who has nail–patella syndrome. She has short stature, dystrophic nails, and absent patellae. The radiograph shows bilateral iliac horns, which were asymptomatic.

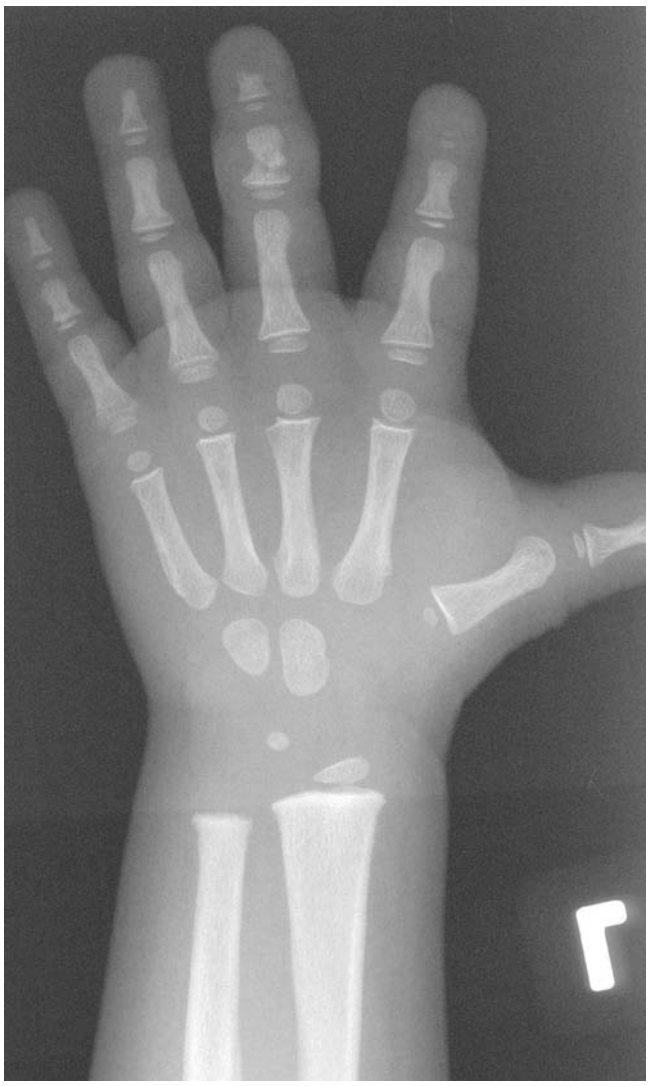


FIGURE 7 AP radiograph of the left hand of a 41/2-year-old boy with pycnodyostosis. Of note are the osteolysis seen in all the distal phalanges and the increased density of the bones, which are both typical of this disorder.

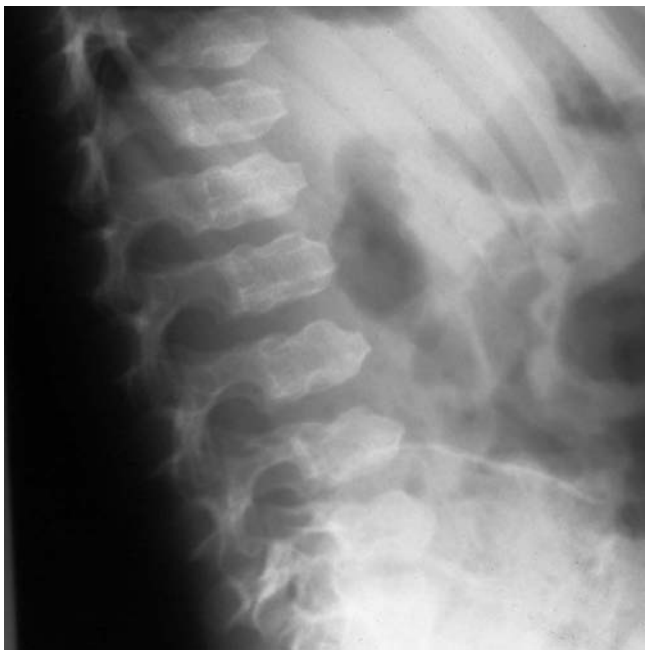


FIGURE 8 Lateral radiograph of the lumbar spine of a teenage girl with Dgyvve–Melchior–Clausen syndrome. She presented with short stature, dysplastic hips, and developmental delay. The spine has a "double-hump" appearance with a central indentation. This is one the few skeletal dysplasias associated with developmental delay.

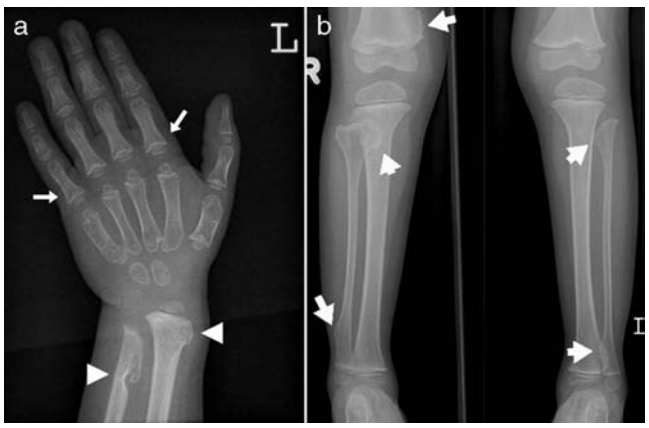


FIGURE 9 (A) Radiograph of the left hand of a 3-year-old boy with Langer–Giedion syndrome (trichorhinophalangeal syndrome type II). He presented with short stature, unusual facies, and severe developmental delay. There are multiple cone epiphyses particularly well seen in the middle phalanges (arrows) and exostoses at both the distal ulna and tibia (arrowheads). (B) Radiograph of the knee demonstrates multiple exostoses at the distal femur and both tibiae and fibulas (arrows).

bone age has been reported in few, such as Desbuquois dysplasia [44]. Cone-shaped epiphyses are a cardinal finding that can help establish a limited differential diagnosis. Cone-shaped epiphysis refers to an epiphysis that is broader at the base than distally and is frequently associated with an indentation in the metaphysis, most often in the phalanges but occasionally in the metacarpals. Experts in this field can recognize 38 types of cones and certain types are specific for distinct disorders [45]. The classic example is type 12 cone epiphyses in the trichorhinophalangeal disorders [46] (Fig. 9). Brachydactyly can be the only radiographic abnormality in certain syndromes (multiple forms have been delineated) or seen as part of a more generalized dysplasia (e.g., Robinow's syndrome) [47].

Campomelia (bowed bones) should not be considered a specific indicator but rather as a starting point for

generating a differential diagnosis. Campomelic dysplasia is named for the bowing seen classically in the femurs and tibiae and associated with an overlying skin dimple. However, the bowing is merely one of the radiographic criteria, and more specific and constant findings are actually seen in the chest, including hypoplastic/aplastic scapulae, hypoplastic thoracic vertebral pedicles, and 11 pairs of thin gracile ribs [48]. Several children with acampomelic campomelic dysplasia due to point mutations in SOX9 or chromosomal rearrangement have been reported [49,50] (Fig. 10). Campomelia is also seen in other dysplasias, such as Stuve–Wiedemann syndrome [51], and more commonly as a reflection of fractures/bone fragility in osteogenesis imperfecta [52]. Campomelia can also be seen in nonskeletal dysplastic conditions, such as Meckel–Gruber syndrome, presumably as a consequence of fetal hypokinesia [53].

Like campomelia, chondrodysplasia punctata is a radiographic sign and not a specific diagnostic entity [54]. The terms chondrodysplasia punctata, stippled epiphyses, and punctate epiphyses have been used interchangeably in the literature. Although this finding will help generate a differential diagnosis, it is seen in more than 20 disorders, including teratogen exposures, intrauterine infections, chromosomal abnormalities, and some metabolic diseases [55]. Punctate epiphyses disappear with age as the multiple calcified centers coalesce, reinforcing the need for an early and complete skeletal survey if a dysplasia is suggested.

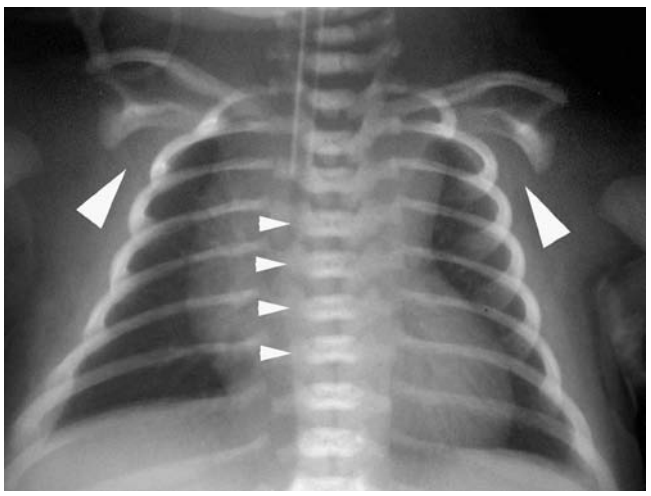


FIGURE 10 AP radiograph of a newborn with campomelic dysplasia. Of note is the absence of vertebral pedicles in the thoracic spine (present in the lumbar spine) and 11 pairs of ribs. A nearly diagnostic and uniform feature is the hypoplastic scapulae (large arrowhead). Not seen here but often present are cervical kyphosis and cervical or thoracic scoliosis.

[AU16]

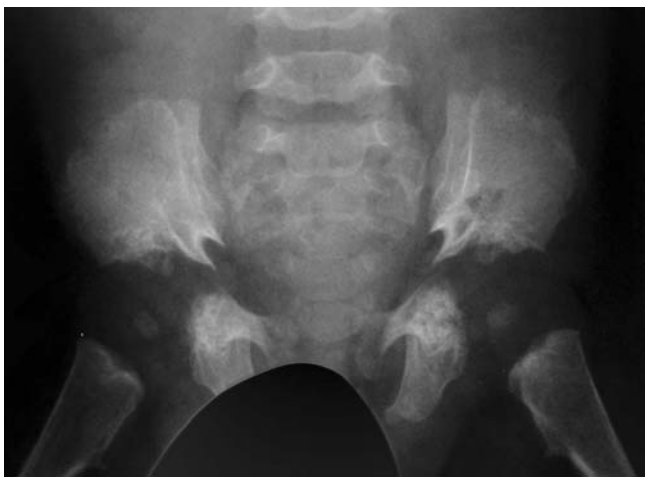


FIGURE 11 The pelvic radiographic findings in asphyxiating thoracic dysplasia (ATD) are important diagnostic features. This radiograph shows the typical pelvis of ATD with narrow sacrosciatic notches and trident appearance of the acetabular roof (radiograph provided by Dr. Elke Schaefer).

Radiographic views of the pelvis can also be important in the differential diagnosis. In a child with ATD, the neonatal manifestations are due to the small chest size, but this does not differentiate ATD from other disorders associated with short, horizontally oriented ribs, such as Barnes syndrome [56]. Although the pelvic abnormalities are clinically silent, they are diagnostically important (Fig. 11). The pelvic abnormalities in some conditions, such as Schneckenbecken and baby rattle dysplasias, are so striking that they have been used in naming the conditions [57,58].

BIOCHEMICAL INVESTIGATIONS

Biochemical investigations are not often useful but in certain instances can be invaluable. Classic examples of dysplasias diagnosed in this manner are the mucopolysacharidoses and mucolipidoses. Screening is done by quantitation of urine mucopolysaccharides and oligosaccharides and diagnosis is by specific enzyme assay on leukocytes or fibroblasts. These disorders have varying degrees of skeletal involvement but follow a pattern known as dysostosis multiplex [59]. The findings in the skull include J-shaped sella turcica and premature fusion of the cranial sutures. The vertebral bodies tend to be ovoid in shape and there can be ossification defects. The ossification defects are pronounced in Morquio syndrome and, along with the platyspondyly, result in the gibbus deformity, which is frequently the presenting sign of the disorder [60] (Fig. 12). There are also characteristic

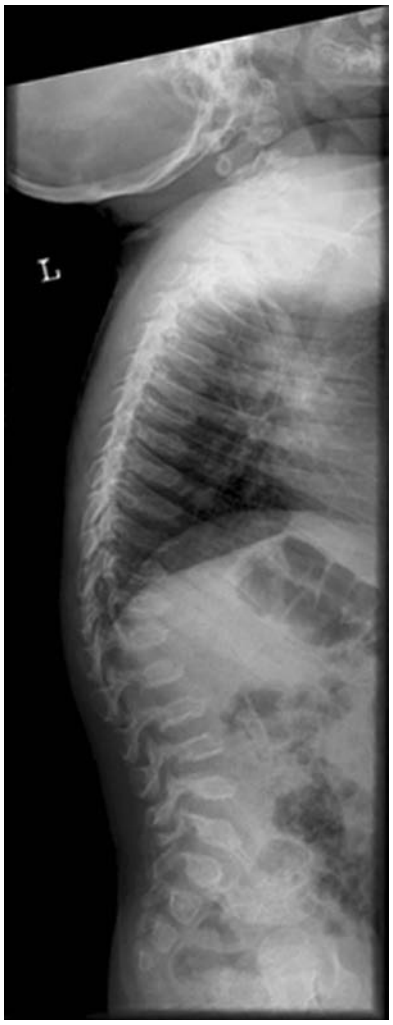


FIGURE 12 Lateral radiograph of a 41/2-year-old boy with Morquio A (*N*-acetyl-galactosamine sulfatase deficiency). In the cervical spine, note the platyspondyly and hypoplastic dens. The lumbar spine is typical of severe dysostosis multiplex, with flattening and midanterior beaking. There is a kyphosis of approximately 15°

changes in the hands, including short proximally pointed metacarpals and bullet-shaped phalanges (Fig. 13). Wide ribs that narrow posteriorly are a frequent sign of dysostosis multiplex [59] (Fig. 14).

Recently, abnormalities in sterol metabolism have been recognized as causing several forms of chondrodysplasia punctata, including chondrodysplasia punctata Conradi–Hunermann and congenital hemidysplasia with icthyosis and limb defects [30,61]. Sterol analysis was useful to show that these were metabolically related disorders and is now used for confirmation of diagnosis [61]. Another example of biochemical analysis is the measurement of GNAS1 function in the diagnosis of Albright hereditary osteodystrophy [62]. Quantitative analysis of this protein's activity in the erythrocyte membrane has been used for diagnosis prior to gene discovery [63].

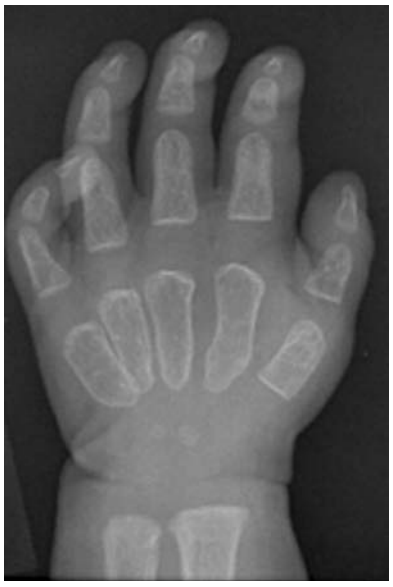


FIGURE 13 Radiograph of the left hand of a 10-month-old boy with Hurler disease (α-iduronidase deficiency). Of note is the marked proximal pointing of the metacarpals, resembling a sharpened pencil.

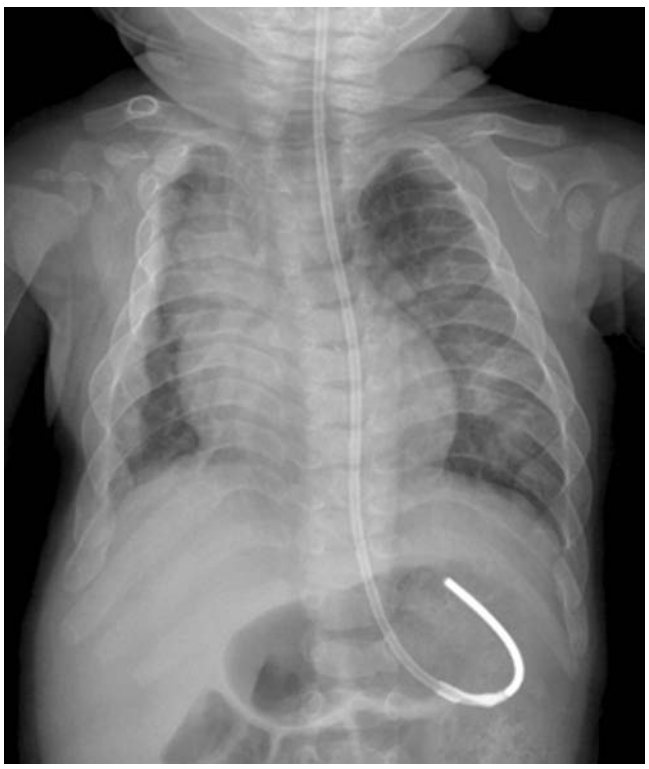
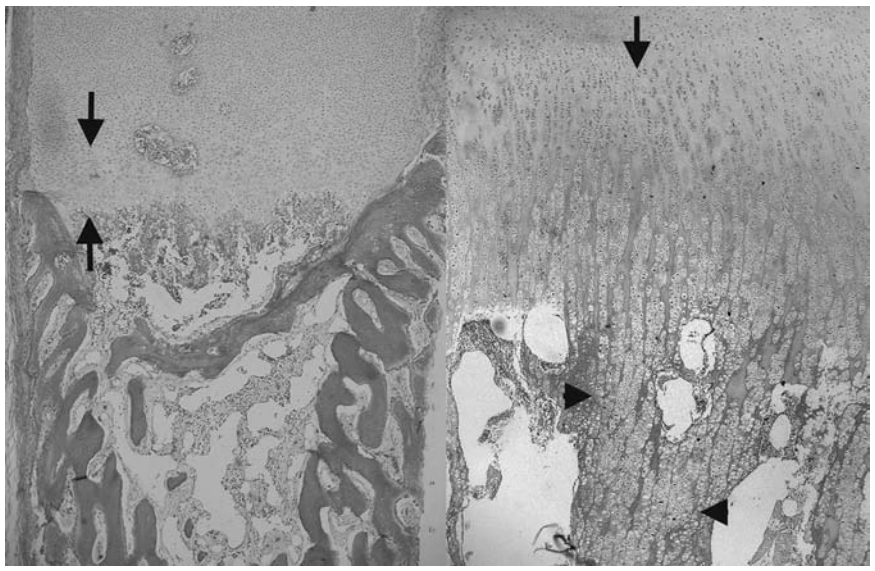


FIGURE 14 Chest radiograph of a 5-month-old girl with I cell disease who died at 7 months of age. Particularly noteworthy is the expansion of the ribs.

CARTILAGE HISTOLOGY

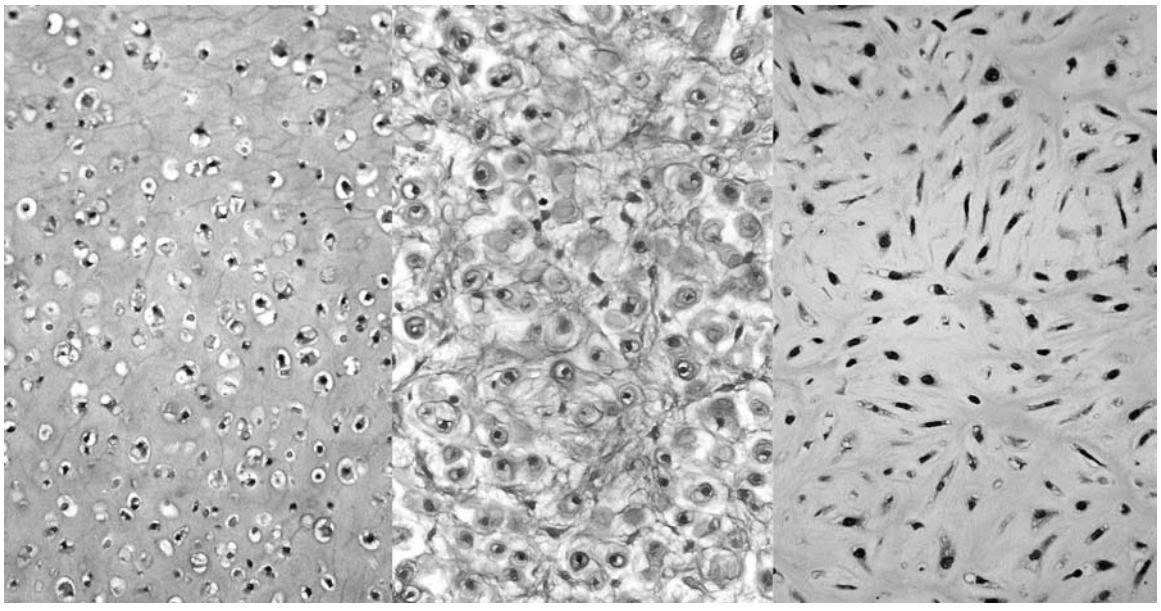
Although not commonly used, histological assessment can be helpful and occasionally crucial to the diagnosis of skeletal dysplasias identified both prenatally and postnatally, especially if the molecular defect is unknown. [AU8] The most useful bone from an autopsy is the femur because it offers bone tissue, cartilage tissue, and two large growth plates. Iliac crest biopsies from living patients can be quite useful. The following are useful criteria for the distinction and diagnosis of bone dysplasias: (i) Where is the primary abnormality—in bone tissue (e.g., osteogenesis imperfecta), in cartilage tissue (e.g., achondrogenesis 1b and 2), or at the growth plate (thanatophoric dysplasia)? (ii) Is the extracellular matrix affected or is it microscopically normal? (iii) Are the chondrocytes morphologically normal or do they show changes in shape (e.g., spindle shaped as in fibrochondrogenesis or ballooned as in collagen 2 dysplasias)? (iv) Within the growth plate, are the relative widths of the columnar zone, the hypertrophic chondrocyte zone, and the provisional calcification zone correct? Routine hematoxyline and eosine staining is of limited value because of the poor affinity of cartilage matrix for these dyes. Whenever possible, Azan–Mallory staining or another trichrome staining method should be performed to visualize collagen fibers, and staining with a cationic azo dye (Alcian blue or toluidine blue) should be performed to visualize the anionic sulfated proteoglycans in the cartilage matrix. To obtain the best visualization of cellular and matrix components, specimens should not be decalcified and embedding should be done in a plastic such as methylmerthacrylate rather than paraffin.

Fibrochondrogenesis is a lethal (presumed autosomal recessive) disorder named for its unusual histological pattern [64]. Radiographically, there is a resemblance to lethal metatropic dysplasia, but microscopic evaluation of the growth plate revealed a very disturbed pattern compared to controls that is particular to fibrochondrogenesis [64,65]. The columnar zone is reduced in width in the thanatophoric dysplasia/achondroplasia group, whereas it can be markedly wider than normal in hypophosphatasia [66] (Fig. 15). The importance of cartilage histology is further demonstrated in the achondrogenesis group: Many of the distinctive radiographic features are not reliably detected in midgestation fetuses, but cartilage histology may allow for reliable distinction between type 1B (normal chondrocytes and rarefied matrix with coarse collagen fibers), type 1A (normal matrix and inclusions in chondrocytes), and type 2 (matrix dehiscence and vacuole formation and ballooned chondrocytes) [67,68] (Fig. 16). These data can be used to decide what confirmatory laboratory investigations should be obtained first.



[AU17]

FIGURE 15 Examples of architectural disturbances at the metaphyses. (Left) Metaphysis of a long bone of a fetus (28 weeks) with thanatophoric dysplasia type 1. The width of the proliferating, columnar chondrocyte zone (between the arrows) is dramatically reduced; column formation is barely recognizable. There is a dense fibrooss-eous band just proximal to the growth zone that correlates with a cupped appearance of the metaphysis on radiographs. (Right) Metaphysis of a long bone of a fetus (33 weeks) with hypophosphatasia. The defect in alkaline phosphatase activity impairs terminal differentiation of the proliferating chondrocytes to hypertrophic chondrocytes. Therefore, column formation is exuberant (some columns can be followed almost to the bottom of the figure). Magnification, approximately 20×.



[AU18]

FIGURE 16 Examples of different patterns of changes in chondrocytes and cartilage matrix in epiphyseal cartilage of fetuses with achondrogenesis type 1A (left) and type 1B (middle) and fibrochondrogenesis (right). (Left) The cartilage matrix in achondrogenesis type 1A is smooth and homogeneous and thus near normal. The chondrocytes have irregular sizes, and in some vacuolization of the cytoplasm can be recognized. Also, some chondrocytes display eosinophilic inclusions (which would show better after PAS staining). (Middle) The cartilage matrix in achondrogenesis type 1B does not have a smooth ground-glass pattern but shows instead coarse collagen fibers that tend to coalesce around the chondrocytes. Some of the chondrocytes show a limited pericellular (territorial) zone with some preservation of matrix. (Right) Fibrochondrogenesis. With this conventional hematoxyline and eosine staining, the main abnormality visible is the spindle-shaped (fibroblast-like) chondrocytes that tend to be grouped in nests separated by fibrous strands.

Although the role of careful histological examination for diagnostic purposes is undisputed, its contribution to suggesting possible pathogenetic mechanisms is controversial because it has been helpful in some cases (e.g., in linking dyssegmental dysplasia to the perlecan gene by virtue of histologic analogies to a perlecan mouse knockout) but misleading in others [69]. For example, histochemical evidence suggesting a proteoglycan defect in achondrogenesis and diastrophic dysplasia has been present for many years, but the disorders were linked only after biochemical and molecular evidence of a common sulfation defect; histochemical data had long been interpreted as suggestive of a collagen 2 defect or a metabolic defect leading to cellular demise in diastrophic dysplasia. The intermediate defect, atelosteogenesis 2, was separated from severe diastrophic dysplasia despite radiographic and histologic evidence of a close relationship between the two.

[AU9]

[AU10]

MOLECULAR BASIS

As the molecular basis has become known for increasingly more skeletal dysplasias, mutation analysis has become an increasingly useful tool for confirmation of the clinical/radiographic diagnosis. The determination of a specific molecular diagnosis can have clinical implications for prognosis of the patient and for recurrence risk for the family. This is particularly important for those disorders that are inherited in an autosomal recessive manner or have significant germline mosaicism and that might be amenable to prenatal diagnosis. Knowledge of the gene defect also allows for the description of the complete spectrum of a disorder and the overlap of certain disorders. For example, it has been shown that recessive metaphyseal dysplasia without hypotrichosis is a variant of CHH and that hair anomalies and immunodefciency are not obligate features of CHH [70]. Similarly, molecular analysis has revealed that Ehlers–Danlos syndrome type 7 is caused by splicing mutations in the type 1 collagen genes, thus explaining the phenotypic overlap between this disorder and osteogenesis imperfecta [71].

[AU11]

PRENATAL DETECTION OF SUSPECTED SKELETAL DYSPLASIA

In recent years, ultrasonographic examination during pregnancy has become part of standard prenatal care,

and measurements of the skull, abdomen, and femurs are a routine part of the exam. Currently, more than 80% of the lethal dysplasias are detected on prenatal ultrasound, and the nonlethal or variably lethal skeletal dysplasias are increasingly detected [72]. The most common findings prompting suspicion of a skeletal dysplasia are short limbs for gestational age or polyhydramnios [73]. Once a skeletal dysplasia is suspected, the patient is referred to a tertiary care center for detailed anatomic screening. Although historically *in utero* radiographs were used to establish a diagnosis, in practice this has been abandoned due to its limitations and the advances in ultrasound technology [74].

Prenatally, it is most important to determine whether or not the fetus actually has a skeletal dysplasia and, if so, whether it is lethal because this will often play a role in pregnancy management. Perinatal lethality in skeletal dysplasias is usually secondary to restrictive lung disease as a consequence of a small bony thorax; thus, measurements of the thoracic circumference and the thoracic/abdominal ratio are the best indicators of lethality [75] (Fig. 17). Severely shortened limbs (micromelia) are a useful but indirect indicator of lethality and can sometimes be appreciated earlier in the pregnancy than small thoracic circumference [75]. However, not all short limbs are due to dysplasia, and intrauterine growth retardation can be mistaken for a skeletal dysplasia. This is important to recognize because it will affect prognosis for the current pregnancy and recurrence risk dependent on the underlying cause of the growth failure [76].

Prenatally, in addition to assessing the individual bones, such as by examining postnatal radiographs, it is necessary to assess the pattern of bony abnormalities. It is more difficult to judge radiographic features prenatally, but an examination of the skeleton and the various patterns seen in dysplasias can help formulate a reasonable differential diagnosis. Ultrasound visualization of a skull defect might lead to the diagnosis of osteogenesis imperfecta or hypophosphatasia. However, a more detailed examination of the fetal skeleton might reveal absent clavicles and delayed ossification of the pubis and lead to the diagnosis of cleidocranial dysplasia [77]. Examination of the fetal head and neck might reveal other clues, such as the kleeblattschadel of thanatophoric dysplasia type II or the micrognathia of the type II collagenopathies [78] (Fig. 18). A detailed ultrasound examination of fetal structures and organs is recommended because ancillary ultrasound findings are helpful in forming the differential diagnosis. Findings includepolyhydramnios, abnormal fetal positioning

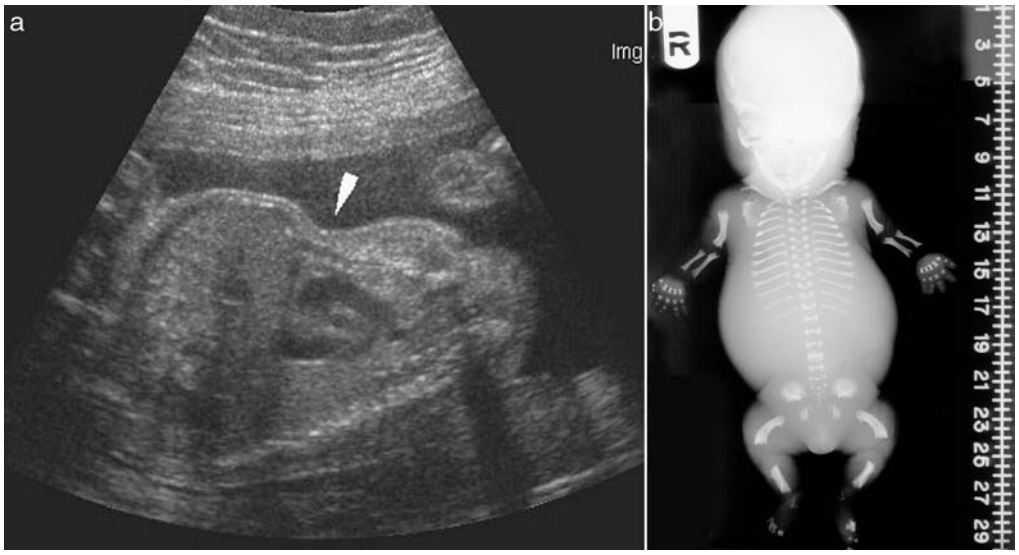


FIGURE 17 (A) Ultrasound performed at 23.5 weeks due to suspicion of skeletal dysplasia. Mildly shortened femurs were noted at 12 weeks and repeat ultrasound at 19 weeks showed micromelia, small thorax, and marked midface hypoplasia. Based on the findings, the parents were counseled that the fetus had a lethal condition and that thanatophoric dysplasia (TD) was the likely diagnosis. This view of the fetus shows the narrow chest diameter compared to the abdomen. After termination of pregnancy, the diagnosis of type 1 was confirmed by radiographs and molecular analysis. (B) Radiograph of the fetus with TDI. This diagnosis was subsequently confirmed by molecular analysis, which showed the C742T mutation in the FGF-R3 gene (typical of TDI). The radiographic findings are severely shortened limbs with trident positioning of the fingers and bowed femurs. In the thorax, there are H-shaped platyspondyly and short ribs. TD is broadly classified into two types. TD1 causes bent/angulated femurs. TD2 is associated with cloverleaf skull caused by multiple craniosynostoses and relatively straight femurs.

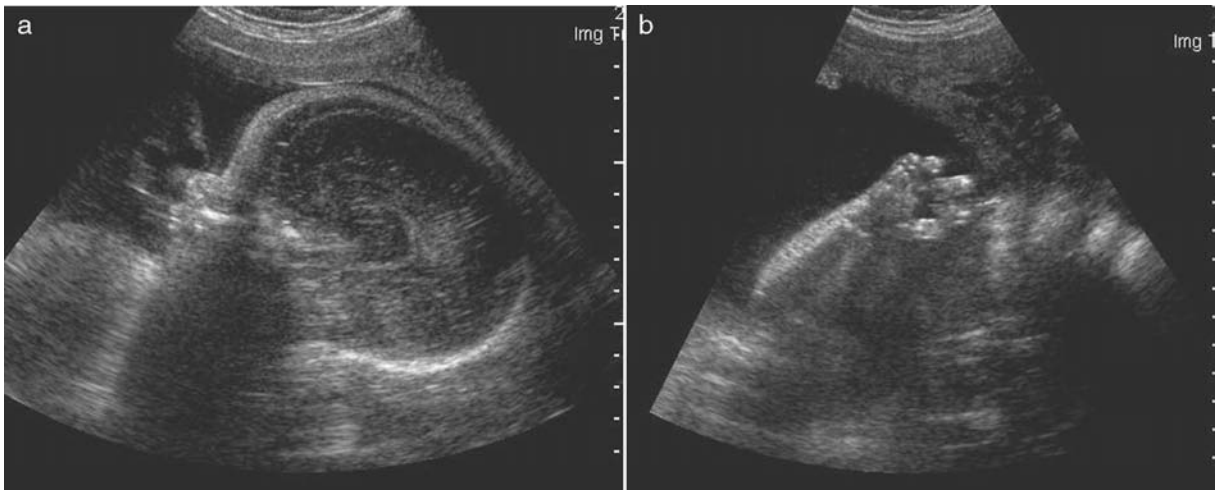


FIGURE 18 A fetus assessed for short limbs at 22 weeks of gestation. Of note, the head was relatively large and on profile had features of achondroplasia. Most noticeable was the prominent forehead and the depressed nasal bridge. (B) On inspection of the extremities, the diagnosis of achondroplasia was supported by the finding of trident hand. The diagnosis was confirmed postnatally.

(e.g., club feet and contractures), and congenital heart defects [76].

Accurate prenatal diagnosis of skeletal dysplasias remains problematic. In order to ensure appropriate counseling, posttermination or postnatal examination should be done, including clinical exam/autopsy and radiographs. Unless a specific diagnosis is highly suspect, molecular testing should be reserved until after delivery or termination of pregnancy to avoid inaccurate prenatal diagnosis leading to "normal" molecular results and false reassurance of the expectant parents.

CONCLUSION

In practice, the diagnosis of skeletal dysplasias is not difficult, but it remains complicated. It demands a familiarity with numerous rare conditions and good pattern-recognition skills. The sequence of steps in this chapter provides a framework for establishing a differential diagnosis, but consultation with an expert in the field of skeletal dysplasia is a key step in refining a suspected diagnosis. Despite advances in molecular medicine, the interpretation of skeletal radiographs is still essential for diagnosis. When the clinician has delineated the pattern of radiographic abnormalities and clinical features, it is possible to search the medical literature and radiographic atlases for a matching pattern. However, as the number of skeletal dysplasias that are molecularly defined increases, mutation analysis is becoming an increasingly more important method of confirming the suspected diagnosis of rare entities. Establishment of a precise and correct diagnosis is important for appropriate counseling regarding potential complications, expected adult height, and recurrence risk.

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