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SKELETAL DYSPLASIAS

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ABSTRACT

Skeletal dysplasias form a complex group of more than 400 conditions with extraordinary clinical and molecular heterogeneity. Their classification changes as we learn about their molecular bases. After a brief introduction to the evaluation of the short child, this chapter is structured according to the 2010 nosology and classification of genetic skeletal disorders and is not intended to detail each rare skeletal dysplasia. Rather, it aims to familiarize the reader with this classification, so that the clinician will be able to determine in which category of conditions to place an affected individual and thus establish a differential diagnosis. We then describe the clinical and radiological manifestations of some of the more common skeletal dysplasias in each group.

INTRODUCTION

Skeletal dysplasias form a complex group of more than 400 conditions with extraordinary clinical and molecular heterogeneity. Their classification changes as we learn about their molecular bases. After a brief introduction to the evaluation of the short child, this chapter is structured according to the 2010 nosology and classification of genetic skeletal disorders (*1*) and is not intended to detail each rare skeletal dysplasia. Rather, it aims to familiarize the reader with this classification, so that the clinician will be able to determine in which category of conditions to place an affected individual and thus establish a differential diagnosis. In the following chapter, we describe the clinical and radiological manifestations of some of the more common skeletal dysplasias in each group. The table for each section lists, when available, the inheritance pattern, the gene, and the OMIM number. General references used include OMIM (www.omim.org), Genereviews (GR, www.ncbi.nlm.nih.gov/books/1116/), Orphanet (www.orpha.net), and chapters or manuscripts by Dr. Spranger (*2, 3*) and Dr. Lachman (*4*). For genetic testing, clinicians are encouraged to refer to the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/) and their local geneticist.

EVALUATION OF THE SHORT CHILD

The first step is to analyze the growth curve of the child, compare it to an ethnicity-appropriate reference and the growth history of the parents. After a thorough familial and clinical history and examination, treatable endocrine and common conditions should be considered. Namely, if there is proportionate short stature with increased weight-for-height ratio, one needs to consider growth hormone deficiency or insensitivity, hypothyroidism, or glucocorticoid excess. Work-up could include measuring bone age, IGF1, IGFBP3, T4, TSH. A karyotype, GH, GHBP, GHRH and ACTH may be

indicated. If there is proportionate short stature with decreased weight-for-height ratio, one needs to consider undernutrition or malnutrition, malabsorption, or a chronic systemic disease. Work-up depends on history and physical examination, but may include a complete blood count with sedimentation rate (for inflammatory bowel disease) and serum tissue transglutaminase (for celiac disease), serum electrolytes and a first-void morning urinalysis (for renal tubular acidosis or nephrogenic diabetes insipidus). A more detailed discussion can be found in a review by Rose et al.(*5*) and other chapters in Endotext.

SKELETAL DYSPLASIA CLASSIFICATION

The first 8 groups of conditions in the 2010 nosology are separated according to the molecular basis of the disease: *FGFR3*, type 2 collagen, type 11 collagen, sulfation disorders, perlecan, aggrecan, filamin, and *TRPV4*. The other 32 groups are organized according to their clinical and radiographic presentation. The prefix *acro-* refers to the extremities (hands and feet), meso- to the middle portion (ulna and radius, tibia and fibula), *rhizo-* to the proximal portion (femur and humerus), *spondylo-* to the spine, *epi-* to the epiphyses, and *meta-* to the metaphyses. For example, if only the hands and feet are shorter, one would consult the acromelic group of conditions, whereas if the spine and metaphyses are affected, one would consult the spondylometaphyseal dysplasias. Listed below are the 40 groups of conditions to be detailed in this chapter.

Groups of conditions organized according to their molecular bases

1. *FGFR3* chondrodysplasia group
2. Type 2 collagen group and similar disorders
3. Type 11 collagen group
4. Sulfation disorders group
5. Perlecan group
6. Aggrecan group
7. Filamin group and related disorders
8. *TRPV4* group

Groups of conditions organized according to their clinical presentations

9. Short-ribs dysplasias (with or without polydactyly) group
10. Multiple epiphyseal dysplasia and pseudoachondroplasia group
11. Metaphyseal dysplasias
12. Spondylometaphyseal dysplasias (SMD)
13. Spondylo-epi-(meta)-physeal dysplasias (SE(M)D)
14. Severe spondylodysplastic dysplasias
15. Acromelic dysplasias (extremities of the limbs)
16. Acromesomelic dysplasias (extremities and middle portion of the limbs)
17. Mesomelic and rhizo-mesomelic dysplasias (proximal and middle portions of the limbs)
18. Bent bones dysplasias
19. Slender bone dysplasia group
20. Dysplasias with multiple joint dislocations
21. Chondrodysplasia punctata (CDP) group
22. Neonatal osteosclerotic dysplasias
23. Increased bone density group (without modification of bone shape)
24. Increased bone density group with metaphyseal and/or diaphyseal involvement
25. Osteogenesis imperfecta and decreased bone density group
26. Abnormal mineralization group
27. Lysosomal storage diseases with skeletal involvement (dysostosis multiplex group)
28. Osteolysis group

29. Disorganized development of skeletal components group
30. Overgrowth syndromes with skeletal involvement
31. Genetic inflammatory/rheumatoid-like osteoarthropathies
32. Cleidocranial dysplasia and isolated cranial ossification defects group
33. Craniosynostosis syndromes
34. Dysostoses with predominant craniofacial involvement
35. Dysostoses with predominant vertebral with and without costal involvement
36. Patellar dysostoses
37. Brachydactylies (with or without extraskeletal manifestations)
38. Limb hypoplasia—reduction defects group
39. Polydactyly-Syndactyly-Triphalangism group
40. Defects in joint formation and synostoses

1. *FGFR3* CHONDRODYSPLASIA GROUP

Thanatophoric dysplasia (thus named because it often results in early death) is characterized by micromelia with bowed femurs, short ribs, narrow thorax, macrocephaly, distinctive facial features, brachydactyly, hypotonia. Radiographically, there is rhizomelic shortening of the long bones with irregular metaphyses, platyspondyly, small foramen magnum with brain stem compression, bowed femurs (TD type I) and cloverleaf skull (always in TD type II; sometimes in TD type I). CNS abnormalities include temporal lobe malformations, hydrocephaly, brain stem hypoplasia and neuronal migration abnormalities.

Figure 1. Thanatophoric dysplasia type 1. Severe platyspondyly, very short ribs narrow thorax, short broad pelvis, large skull, very short and bent long bones.

Achondroplasia is characterized by small stature with rhizomelia and redundant skin folds, limitation of elbow extension and genu varum, short fingers with trident configuration of the hands. Craniocervical junction compression is a major complication which may occur and requires surveillance for early detection and management. There is also thoracolumbar kyphosis, lumbar lordosis, and a large head with frontal bossing with midface hypoplasia. The radiographic findings include short tubular bones with metaphyseal flaring, narrowing of the interpediculate distance of the lumbar spine, rounded ilia and horizontal acetabula, narrow sacrosciatic notch and proximal femoral radiolucency. In hypochondroplasia, there are similar but milder clinical and radiological findings, the head is large but there is no midface hypoplasia.

Figure 2. Achondroplasia. Small rounded iliac bones, horizontal acetabula, decreasing interpediculate distance, normal vertebral body height, short ribs.
Figure 3. Hypochondroplasia. Decreased interpediculate distance, short broad long bones , short wide femoral necks, relative elongation of the distal fibula compare to tibia.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Thanatophoric dysplasia type 1 (TD1)	AD	187600	1366	1860	*FGFR3*
Thanatophoric dysplasia type 2 (TD2)	AD	187601	1366	93274	*FGFR3*
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	AD	187600	1455	85165	*FGFR3*
Achondroplasia	AD	100800	1152	15	*FGFR3*
Hypochondroplasia	AD	146000	1477	429	*FGFR3*
Camptodactyly, tall stature, and hearing loss syndrome (CATSHL)	AD	610474			*FGFR3*

Please also refer to group 33 for craniosynostoses syndromes linked to FGFR3 mutations, as well as LADD syndrome in group 39 for another FGFR3-related phenotype.

2. TYPE 2 COLLAGEN GROUP

Stickler syndrome is characterized by ocular findings of myopia, cataract, and retinal detachment, sensorineural and conductive hearing loss, flat mala and cleft palate (alone or as part of the Robin sequence), mild spondyloepiphyseal dysplasia and early-onset arthritis (*6*).

Figure 4. Stickler syndrome. small epiphyses, wide femoral neck, hypoplastic iliac wings, flat epiphyses, schmorl's nodules.
Spondyloepiphyseal dysplasia congenita (SEDC) presents with disproportionate short stature (short trunk), abnormal epiphyses, and flattened vertebral bodies. Some features of Stickler syndrome include myopia and/or retinal degeneration with retinal detachment and cleft palate.

Figure 5. SED congenita. Platyspondyly, delayed epiphyseal ossification (especially femoral heads), dens hypoplasia.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Achondrogenesis type 2 (ACG2; Langer-Saldino)	AD	200610		93296	*COL2A1*
Platyspondylic dysplasia, Torrance type	AD	151210		85166	*COL2A1*
Hypochondrogenesis	AD	200610		93296	*COL2A1*
Spondyloepiphyseal dysplasia congenita (SEDC)	AD	183900		94068	*COL2A1*
Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type	AD	184250		93346	*COL2A1*
Kniest dysplasia	AD	156550		485	*COL2A1*
Spondyloperipheral dysplasia	AD	271700		1856	*COL2A1*
Mild SED with premature onset arthrosis	AD				*COL2A1*
SED with metatarsal shortening (formerly Czech dysplasia)	AD	609162		137678	*COL2A1*
Stickler syndrome type 1	AD	108300	1302	828	*COL2A1*

3. TYPE 11 COLLAGEN GROUP

Marshall syndrome resembles Stickler syndrome but is characterized by a flat or retracted midface, thick calvaria, abnormal frontal sinuses with shallow orbits, intracranial calcifications, and ectodermal abnormalities including abnormal sweating and teeth.

Otospondylomegaepiphyseal dysplasia (OSMED) is characterized by sensorineural hearing loss, enlarged epiphyses, skeletal dysplasia with disproportionately short limbs, vertebral body anomalies, midface hypoplasia, a short nose with anteverted nares and a flat nasal bridge, a long philtrum, cleft palate/bifid uvula, micrognathia, and hypertelorism.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Stickler syndrome type 2	AD	604841	1302	90654	*COL11A1*
Marshall syndrome	AD	154780		560	*COL11A1*
Fibrochondrogenesis	AR	228520		2021	*COL11A1*
Otospondylomegaepiphyseal dysplasia (OSMED),	AR	215150		1427	*COL11A2*

recessive type					
Otospondylomegaepiphyseal dysplasia (OSMED), dominant type (Weissenbacher-Zweymüller syndrome, Stickler syndrome type 3)	AD	215150		1427	*COL11A2*

Please also refer to Stickler syndrome type 1 in group 2

4. SULFATION DISORDERS GROUP

Achondrogenesis type 1B (ACG1B) is characterized extremely short limbs with short fingers and toes, hypoplasia of the thorax, protuberant abdomen, and hydropic fetal appearance. There is a normal-sized skull with a flat facies. There is a lack of ossification of the vertebral bodies (except for pedicles), short and thin ribs, and ossification of the upper part of iliac bones giving crescent-shaped appearance. Shortening of the tubular bones with metaphyseal spurring ("thorn apple" appearance) is seen.

The clinical features of diastrophic dysplasia (DTD) include limb shortening with hitchhiker thumbs, ulnar deviation of the fingers, a gap between the first and second toes, clubfeet, contractures of large joints, early-onset osteoarthritis and radial dislocation. The skull is normal-sized. There is some trunk shortening, a small chest with a protuberant abdomen and spinal deformities (scoliosis, exaggerated lumbar lordosis, cervical kyphosis). Non-skeletal findings include a cleft palate, cystic ear swelling in the neonatal period, and flat hemangiomas of the forehead.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Achondrogenesis type 1B (ACG1B)	AR	600972	1516	93298	*SLC26A2*
Atelosteogenesis type 2 (AO2)	AR	256050	1317	56304	*SLC26A2*
Diastrophic dysplasia (DTD)	AR	222600	1350	628	*SLC26A2*
MED, autosomal recessive type (rMED; EDM4)	AR	226900	1306	93307	*SLC26A2*
SEMD, PAPSS2 type	AR	603005		93282	*PAPSS2*
Chondrodysplasia with congenital joint dislocations, CHST3 type (recessive Larsen syndrome)	AR	608637	62112	263463	*CHST3*
Ehlers-Danlos syndrome, CHST14 type (“musculo-skeletal variant”)	AR	601776		2953	*CHST14*

Please also refer to groups 7 and 26 for other conditions with multiple dislocations

5. PERLECAN GROUP

Schwartz-Jampel syndrome manifests with myotonia (characteristic facies with blepharophimosis and a puckered facial appearance) and osteoarticular abnormalities with progressive joint stiffness. There is also a flattening of the vertebral bodies, short stature, hip dysplasia, bowing of the diaphyses and irregular epiphyses.

Group/name of disorder	Inher.	OMIM	Orpha	Gene
Dyssegmental dysplasia, Silverman-Handmaker type	AR	224410	1865	*HSPG2*
Dyssegmental dysplasia, Rolland-Desbuquois type	AR	224400	156731	*HSPG2*
Schwartz-Jampel syndrome (myotonic chondrodystrophy)	AR	255800	800	*HSPG2*

6. AGGRECAN GROUP

These conditions have been each described in one family and will not be discussed in detail here.

Group/name of disorder	Inher.	OMIM	Orpha	Gene
SED, Kimberley type	AD	608361	93283	*ACAN*
SEMD, Aggrecan type	AR	612813	171866	*ACAN*
Familial osteochondritis dissecans	AD	165800	251262	*ACAN*

7. FILAMIN GROUP AND RELATED DISORDERS

The otopalatodigital (OPD) spectrum disorders caused by *FLNA* mutations include Otopalatodigital syndromes type I and II, frontometaphyseal dysplasia, Melnick-Needles syndrome and terminal osseous dysplasia with pigmentary skin defects (TODPD). Manifestations include abnormal facial features (such as widely spaced eyes), hypoplasia of the thorax, scoliosis, shortened digits, bowed long bones and joint movement limitations.

Larsen syndrome is characterized by large-joint dislocations (hip, knee, and elbow) and characteristic craniofacial abnormalities (prominent forehead, depressed nasal bridge, flattened midface, and ocular hypertelorism). There can also be club feet (equinovarus or equinovalgus foot deformities); scoliosis and cervical kyphosis, cervical myelopathy; and spatula-shaped fingers, most marked in the thumb.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Frontometaphyseal dysplasia	XLD	305620	1393	1826	*FLNA*
Osteodysplasty Melnick-Needles	XLD	309350	1393	2484	*FLNA*
Otopalatodigital syndrome type 1 (OPD1)	XLD	311300	1393	90650	*FLNA*
Otopalatodigital syndrome type 2 (OPD2)	XLD	304120	1393	90652	*FLNA*
Terminal osseous dysplasia with pigmentary defects (TODPD)	XLD	300244	1393	88630	*FLNA*
Atelosteogenesis type 1 (AO1)	AD	108720	2534	1190	*FLNB*
Atelosteogenesis type 3 (AO3)	AD	108721	2534	56305	*FLNB*
Larsen syndrome (dominant)	AD	150250	2534	503	*FLNB*
Spondylo-carpal-tarsal dysplasia	AR	272460	2534	3275	*FLNB*
Spondylo-carpal-tarsal dysplasia	AR	272460		3275	
Franck-ter Haar syndrome	AR	249420		137834	*SH3PXD2B*

Please also refer to group 4 for recessive Larsen syndrome and group 26 for conditions with multiple dislocations.

8. *TRPV4* GROUP

Metatropic dysplasia is a severe spondyloepimetaphyseal dysplasia characterized in infancy by a long trunk and short limbs with limitation and enlargement of joints and usually severe kyphoscoliosis. The term metatropic comes from the Greek metatropos, and refers to the changing pattern of the skeletal anomalies. Indeed, there is progressive kyphoscoliosis which leads to a shortened trunk. Radiologic features include platyspondyly, metaphyseal enlargement, and shortening of long bones.

Spondylometaphyseal dysplasia, Kozlowski type is characterized by short-trunked short stature, metaphyseal abnormalities in the femur (prominent in the femoral neck and trochanteric area) with coxa vara, scoliosis and platyspondyly.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene

Metatropic dysplasia	AD	156530		2635	*TRPV4*
Spondyloepimetaphyseal dysplasia, Maroteaux type (Pseudo-Morquio syndrome type 2)	AD	184095		263482	*TRPV4*
Spondylometaphyseal dysplasia, Kozlowski type	AD	184252		93314	*TRPV4*
Brachyolmia, autosomal dominant type	AD	113500		93304	*TRPV4*
Familial digital arthropathy with brachydactyly	AD	606835		85169	*TRPV4*

9. SHORT-RIBS DYSPLASIAS (WITH OR WITHOUT POLYDACTYLY) GROUP

The short rib-polydactyly syndromes (SRPS) are ciliopathies characterized by short ribs, short limbs, polydactyly, and multiple anomalies of major organs, including heart, intestines, genitalia, kidney, liver, and pancreas. In SRPS I (Saldino-Noonan type), the long bones are torpedo-shaped; in SRPS III (Verma-Naumoff type) they are banana-peel shaped. In SRPS II (Majewski syndrome) the tibiae are short and oval, and in SRPS VI (Beemer type), the tibiae are not as short and polydactyly is rare (*7*).

In asphyxiating thoracic dystrophy (Jeune syndrome), there is a severely constricted thoracic cage, short-limbed short stature, polydactyly, retinal degeneration and pancreatic cysts.

Figure 6. Asphyxiating thoracic dystrophy. Short ribs long and narrow chest, small pelvis, trident acetabula, no platyspondyly (helps differentiate from thanatophoric dysplasia), cystic renal disease.

Ellis-van Creveld syndrome is characterized by short limbs, short ribs, postaxial polydactyly, and dysplastic nails and teeth.

Figure 7. Chondroectodermal dysplasia (or Ellis-van Creveld syndrome). Short ribs, early ossification of femoral head, polydactyly cone-shaped epiphyses, no platyspondyly (helps differentiate from thanatophoric dysplasia), flatening of lateral aspect of proximal tibial epiphysis.

In uniparental disomy of paternal chromosome 14, there is a narrow, bell-shaped thorax with caudal bowing of the anterior ribs and cranial bowing of the posterior ribs (coat hanger appearance) (*8*), and flaring of the iliac wings. There are also joint contractures, dysmorphic facial features, and developmental delay/intellectual deficiency.

Group/name of disorder	**Inher.**	**OMIM**	**Orpha**	**Gene**
Chondroectodermal dysplasia (Ellis-van Creveld)	AR	225500	289	*EVC1, ECV2, LBN*
Short rib—polydactyly syndrome (SRPS) type 1/3 (Saldino-Noonan/Verma-Naumoff)	AR	263510	93271	*DYNC2H1*
SRPS type 1/3 (Saldino-Noonan)	AR	263510	93271	*IFT80*
SRPS type 2 A	AR	263520	93269	*NEK1*
SRPS type 2B	AR	615087	93269	*DYNC2H1*
SRPS type 3 Verma-Naumoff	AR	263510	93271	*DYNC2H1*
SRPS type 4 (Beemer)	AR	269860	93268	
SRPS type 5	AR	614091		*WDR35*
Uniparental disomy of paternal chromosome 14 (UPD14)		608149	96334	*Complete chromosome 14*
Cerebrocostomandibular syndrome	AR/AD	117650	1393	*SNRPB*
Oral-facial-digital syndrome type 4 (Mohr-Majewski)	AR	258860	2753	*TCTN3*

Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	208500	474	*TTC21B, IFT80, WDR19, DYNC2H1, ATD*
Thoracolaryngopelvic dysplasia (Barnes)	AD	187760	3317	

10. MULTIPLE EPIPHYSEAL DYSPLASIA AND PSEUDOACHONDROPLASIA GROUP

Multiple epiphyseal dysplasia is usually not recognizable before 1-2 years of age (*9*). Then, joint pain at the hips and knees is noted after physical exercise. Mild to moderate short stature is seen by 5-6 years of age. Radiologically, there is bilateral necrosis of the femoral heads, and the epiphyses of tubular bones, (including metacarpals, metatarsals and phalanges) show maturational delay. Femoral and phalangeal epiphyses are rounded (*COMP*) or flat (*SCL26A2,* see group 4). Double-layered patellae can be seen (*SCL26A2*). The most frequently mutated genes are *COMP* and *SCL26A2*, then the genes encoding type 9 collagen and Matrillin 3.

Figure 8. Multiple epiphyseal dysplasia. Flattened epiphyses, normal spine (no platyspondyly).

Figure 9. Pseudoachondroplasia. Small femoral head, irregular epiphyses, platyspondyly with anterior tongues of vertebral bodies, irregular acetabula.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Pseudoachondroplasia (PSACH)	AD	177170	1487	750	*COMP*
Multiple epiphyseal dysplasia (MED) type 1 (EDM1)	AD	132400	1123	93308	*COMP*
Multiple epiphyseal dysplasia (MED) type 2 (EDM2)	AD	600204	1123	166002	*COL9A2*
Multiple epiphyseal dysplasia (MED) type 3 (EDM3)	AD	600969	1123	166002	*COL9A3*
Multiple epiphyseal dysplasia (MED) type 5 (EDM5)	AD	607078	1123	93311	*MATN3*
Multiple epiphyseal dysplasia (MED) type 6 (EDM6)	AD	614135	1123	166002	*COL9A1*
Multiple epiphyseal dysplasia (MED), other types			1123		
Stickler syndrome, recessive type	AR	614134	1302	250984	*COL9A1*
Familial hip dysplasia (Beukes)	AD	142669	1123	2114	*UFSP2*
Multiple epiphyseal dysplasia with microcephaly and nystagmus (Lowry-Wood)	AR	226960		1824	

Please also refer to multiple epiphyseal dysplasia, recessive type (rMED; EDM4) in sulfation disorders (group 4), familial osteochondritis dissecans in the aggrecan group, as well as ASPED in the Acromelic group

11. METAPHYSEAL DYSPLASIAS

Cartilage-hair hypoplasia manifests with severe disproportionate short-limbed short stature with short hands, bowed femorae and tibiae, joint hypermobility and often metaphyseal dysplasia and large, round epiphyses during childhood, bullet-shaped middle phalanges and vertebral dysplasia. Non-skeletal findings include fine silky slow growing hair, immunodeficiency manifested by an increased rate of infections, anemia, gastrointestinal dysfunction, and an increased risk for malignancy.

Figure 10. Cartilage-hair hypoplasia. Widening of the growth plate (often focal), metaphyseal cupping and irregularity with cyst-like lucencies, short metacarpals and phalanges with cupping and cone-shaped epiphyses.

Shwachman-Diamond syndrome manifests with exocrine pancreatic insufficiency with malabsorption, malnutrition, and growth failure, hematologic abnormalities, including increased risk of malignant transformation, and skeletal abnormalities which include short stature, generalized osteopenia, with delayed appearance of secondary ossification centers (delayed bone age) metaphyseal chondrodysplasia (metaphyses wide and irregular) and finally thickening and irregularity of the growth plates.

Schmid type of metaphyseal chondrodyplasia manifests with short stature, widened growth plates, bowing of the long bones and resembles a milder form of Jansen type metaphyseal chondrodysplasia. Radiological signs include enlarged capital femoral epiphysis in early childhood, coxa vara, greater involvement of the distal femoral metaphysis than the proximal (these disappear after epiphyseal fusion), anterior rib changes and a normal spine.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Metaphyseal dysplasia, Schmid type (MCS)	AD	156500		174	*COL10A1*
Cartilage-hair hypoplasia (CHH; metaphyseal dysplasia, McKusick type)	AR	250250	84550	175	*RMRP*
Metaphyseal dysplasia, Jansen type	AD	156400		33067	*PTHR1*
Eiken dysplasia	AR	600002		79106	*PTHR1*
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman-Diamond syndrome)	AR	260400	1756	811	*SBDS*
Metaphyseal anadysplasia type 1	AD, AR	602111		1040	*MMP13*
Metaphyseal anadysplasia type 2	AR	613073		1040	*MMP9*
Metaphyseal dysplasia, Spahr type	AR	250400		2501	*MMP13*
Metaphyseal acroscyphodysplasia (various types)	AR	250215		1240	
Genochondromatosis (type 1/type 2)	AD/SP	137360		85197	
Metaphyseal chondromatosis with d-2-hydroxyglutaric aciduria	AR/SP	614875		99646	*IDH1*

12. SPONDYLOMETAPHYSEAL DYSPLASIAS (SMD)

SMD Sutcliffe type presents with proportional mild short stature. The spine shows odontoid hypoplasia, hyperconvex vertebral body endplates (lower thoracic and upper lumbar) with an appearance of anterior wedging and no platyspondyly or kyphoscoliosis. Hips show progressive coxa vara with short femoral necks leading to a waddling gait. Metaphyseal abnormalities include flakelike, triangular, or curvilinear ossification centers at the edges of the metaphyses simulating “corner fractures” of long tubular bones, distal tibial metaphyses on the ulnar aspect of the distal radius and in the proximal humerus. Some patients have been reported to have *COL2A1* mutations.

Group/name of disorder	Inher.	OMIM	Orpha	Gene
Spondyloenchondrodysplasia (SPENCD)	AR	271550	1855	*ACP5*
Odontochondrodysplasia (ODCD)	AR	184260	166272	
Spondylometaphyseal dysplasia, Sutcliffe type or corner fractures type	AD	184255	93315	*COL2A1*
SMD with severe genu valgum	AD	184253	93316	
SMD with cone-rod dystrophy	AR	608940	85167	*PCYT1A*
SMD with retinal degeneration, axial type	AR	602271	168549	

Dysspondyloenchondromatosis	SP		85198	*COL2A1*
Cheiro-spondyloenchondromatosis	SP		99647	

Please also refer to SMD Kozlowski (group TRPV4) disorders in group 11 as well as SMD Sedaghatian type in group 12; there are many individual reports of SMD variants

13. SPONDYLO-EPI-(META)-PHYSEAL DYSPLASIAS (SE(M)D)

Spondyloepiphyseal dysplasia tarda manifests with disproportionately short stature and a short trunk. Affected males exhibit retarded growth from about six years of age. Progressive joint and back pain with osteoarthritis follows, involving the larger joints more than the small joints. Radiologically, there are multiple epiphyseal abnormalities, platyspondyly, narrow disc spaces, scoliosis, hypoplastic odontoid process, short femoral necks and coxa vara.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Dyggve-Melchior-Clausen dysplasia (DMC)	AR	223800		239	*DYM*
Immuno-osseous dysplasia (Schimke)	AR	242900	1376	1830	*SMARCAL1*
SED, Wolcott-Rallison type	AR	226980		1667	*EIF2AK3*
SEMD, Matrilin type	AR	608728		156728	*MATN3*
SEMD, short limb—abnormal calcification type	AR	271665		93358	*DDR2*
SED tarda, X-linked (SED-XL)	XLR	313400	1145	93284	*SEDL*
Spondylo-megaepiphyseal-metaphyseal dysplasia (SMMD)	AR	613330		228387	*NKX3-2*
Spondylodysplastic Ehlers-Danlos syndrome	AR	612350		157965	*SLC39A13*
SPONASTRIME dysplasia	AR	271510		93357	
SEMD with joint laxity (SEMD-JL) leptodactylic or Hall type	AD	603546		93360	*KIF22*
SEMD with joint laxity (SEMD-JL) Beighton type	AR	271640		93359	*B3GALT6*
Platyspondyly (brachyolmia) with amelogenesis imperfecta	AR	601216		2899	*LTBP3*
Late onset SED, autosomal recessive type	AR	609223		93284	
Brachyolmia, Hobaek type	AR	271530		93301	*PAPSS2*
Brachyolmia, Toledo type	AR	271630		93303	*PAPSS2*

Please also refer to Brachyolmia (group 8), Opsismodysplasia (group 14), SEMDs (group 11), mucopolysaccharidosis type 4 (Morquio syndrome) and other conditions in group 26, as well as PPRD (SED with progressive arthropathy) in group 31

14. SEVERE SPONDYLODYSPLASTIC DYSPLASIAS

In opsismodysplasia, there is a large anterior fontanelle, anteverted nostrils, pelvic bone anomalies, metaphyseal cupping, delayed ossification, shortened digits, hypotonia, and early death.

Group/name of disorder	Inher.	OMIM	Orpha	Gene
Achondrogenesis type 1A (ACG1A)	AR	200600	93299	*TRIP11*
Schneckenbecken dysplasia	AR	269250	3144	*SLC35D1*
Spondylometaphyseal dysplasia, Sedaghatian type	AR	250220	93317	*GPX4*
Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like)	AR			*SBDS*

Opsismodysplasia	AR	258480	2746	*INPPL1*

Please also refer to Thanatophoric dysplasia, types 1 and 2 (group 1); ACG2 and Torrance dysplasia (group 2); Fibrochondrogenesis (group 3); Achondrogenesis type 1B (ACG1B, group 4); and Metatropic dysplasia (TRPV4 group).

15. ACROMELIC DYSPLASIAS

In Trichorhinophalangeal syndromes, skeletal abnormalities include a short stature, cone-shaped epiphyses at the phalanges, hip malformations, and short stature. All phalanges, metacarpals and metatarsal bones are shortened. Non-skeletal features include sparse scalp hair, bulbous tip of the nose, long flat philtrum, thin upper vermilion border, and protruding ears.

Figure 11. Trichorhinophalangeal syndrome. Shortened phalanges and metacarpals, cone-shaped epiphyses.

In Geleophysic dysplasia, there is short stature, short hands and feet, progressive joint limitation and contractures, distinctive facial features ("smiling" round and full face, small nose with anteverted nostrils, a broad nasal bridge, hypertelorism, long flat philtrum, and a thin upper lip), progressive cardiac valvular disease, and thickened skin.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Trichorhinophalangeal dysplasia types 1/3	AD	190350		77258	*TRPS1*
Trichorhinophalangeal dysplasia type 2 (Langer-Giedion)	AD	150230		502	*TRPS1 andEXT1*
Acrocapitofemoral dysplasia	AR	607778		63446	*IHH*
Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1	AR	218330		1515	*IFT122*
Cranioectodermal dysplasia (Levin-Sensenbrenner) type 2	AR	613610		1515	*WDR35*
Geleophysic dysplasia	AR	231050	11168	2623	*ADAMTSL2*
Geleophysic dysplasia, other types	AR	614185	11168	2623	*FBN1*
Acromicric dysplasia	AD	102370		969	*SMAD4*
Acrodysostosis type 1	AD	101800		950	*PRKAR1A*
Acrodysostosis type 2	AD	614613		950	*PDE4D*
Angel-shaped phalango-epiphyseal dysplasia (ASPED)	AD	105835		63442	
Saldino-Mainzer dysplasia	AR	266920		140969	*IFT140*
Myhre syndrome	AD	139210		2588	*SMAD4*
Weill-Marchesani syndrome type 1	AR	277600	1114	3449	*ADAMTS10*
Weill-Marchesani syndrome type 2	AD	608328	1114	2084	*FBN1*

Please also refer to the short rib dysplasias group

16. ACROMESOMELIC DYSPLASIAS

In Acromesomelic dysplasia, type Maroteaux, there is disproportionate shortening the middle segments (forearms and forelegs) and distal segments (hands and feet) of the appendicular skeleton. There are short broad fingers, shortening of the middle long bones with a bowed radius, and wedging of vertebral bodies.

Group/name of disorder	Inher.	OMIM	Orpha	Gene
Acromesomelic dysplasia type Maroteaux (AMDM)	AR	602875	40	*NPR2*
Grebe dysplasia	AR	200700	2098	*GDF5*
Fibular hypoplasia and complex brachydactyly (Du Pan)	AR	228900	2639	*GDF5*
Acromesomelic dysplasia with genital anomalies	AR	609441		*BMPR1B*
Acromesomelic dysplasia, Osebold-Remondini type	AD	112910	93382	
Acromesomelic dysplasia, Hunter-Thomson type	AR	201250	968	*GDF5*

17. MESOMELIC AND RHIZO-MESOMELIC DYSPLASIAS

Leri-Weill dyschondrosteosis is characterized by short stature, mesomelia, and Madelung wrist deformity (abnormal alignment of the radius, ulna, and carpal bones at the wrist - more common and severe in females).

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Dyschondrosteosis (Leri-Weill)	Pseudo-AD	127300	1215	240	*SHOX*
Langer type (homozygous dyschondrosteosis)	Pseudo-AR	249700	1215	2632	*SHOX*
Omodysplasia	AR	258315		93329	*GPC6*
Robinow syndrome, recessive type	AR	268310	1240	1507	*ROR2*
Robinow syndrome, dominant type	AD	180700		3107	*WNT5A*
Mesomelic dysplasia, Korean type	AD				
Mesomelic dysplasia, Kantaputra type	AD	156232		1836	
Mesomelic dysplasia, Nievergelt type	AD	163400		2633	
Mesomelic dysplasia, Kozlowski-Reardon type	AR	249710		2631	
Mesomelic dysplasia with acral synostoses (Verloes-David-Pfeiffer type)	AD	600383		2496	*SULF1, SLCO5A1*
Mesomelic dysplasia, Savarirayan type (Triangular Tibia-Fibular Aplasia)	SP	605274		85170	

18. BENT BONES DYSPLASIAS

Campomelic dysplasia is characterized by bowed, short and fragile long bones, clubfeet, pelvis and chest abnormalities and eleven pairs of ribs. Non-skeletal anomalies include a flat face, laryngotracheomalacia, Pierre Robin sequence with cleft palate, ambiguous genitalia in males, and brain, heart and kidney malformations.

Figure 12. Campomelic dysplasia. Bell-shaped thorax, hypoplastic scapula, bowed femurs, widely-spaced ischial bones.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Campomelic dysplasia (CD)	AD	114290	1760	140	*SOX9*
Stüve-Wiedemann dysplasia	AR	601559		3206	*LIFR*
Kyphomelic dysplasia, several forms		211350		1801	

Bent bones at birth can be seen in osteogenesis imperfecta, Antley-Bixler syndrome, cartilage-hair hypoplasia, Cummings syndrome, hypophosphatasia, dyssegmental dysplasia, TD, ATD, and other conditions.

19. SLENDER BONE DYSPLASIA GROUP

In Three M (3M) syndrome, there is severe prenatal and postnatal growth retardation, distinctive facial features (large head, triangular face, hypoplastic midface, full eyebrows, fleshy nose tip, long philtrum, prominent mouth and lips, and pointed chin), and normal mental development. The main skeletal anomalies are slender long bones and ribs, foreshortened vertebral bodies, and delayed bone age. Joint hypermobility, joint dislocation, winged scapulae, and pes planus can also be seen.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
3-M syndrome (3M1)	AR	273750	1481	2616	*CUL7*
3-M syndrome (3M2)	AR	612921	1481	2616	*OBSL1*
Kenny-Caffey dysplasia type 1	AR	244460		93324	*TBCE*
Kenny-Caffey dysplasia type 2	AD	127000		93325	*FAM111A*
Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1)	AR	210710		2636	*RNU4ATAC*
Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type)	AR	210720		2637	*PCNT2*
IMAGE syndrome (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies)	XL/AD	614732		85173	*CDKN1C*
Osteocraniostenosis	SP	602361		2763	*FAM111A*
Hallermann-Streiff syndrome	AR	234100		2108	*GJA1*

Please also see Cerebro-arthro-digital dysplasia.

20. DYSPLASIAS WITH MULTIPLE JOINT DISLOCATIONS

Desbuquois dysplasia is characterized by short stature of prenatal onset affecting the rhizomelic and mesomelic portion of the limbs, marked joint laxity, kyphoscoliosis and facial dysmorphisms (round flat face, prominent eyes, and midface hypoplasia)

Group/name of disorder	Inher.	OMIM	Orpha	Gene
Desbuquois dysplasia (with accessory ossification center in digit 2)	AR	251450	1425	*CANT1*
Desbuquois dysplasia with short metacarpals and elongated phalanges (Kim type)	AR	251450	1425	*CANT1*
Desbuquois dysplasia (other variants with or without accessory ossification center)	AR			
Pseudodiastrophic dysplasia	AR	264180	85174	

Please also refer to SED with congenital dislocations, CHST3 type (group 4); Atelosteogenesis type 3 and Larsen syndrome (group 6); SEMDs with joint laxity (group 11)

21. CHONDRODYSPLASIA PUNCTATA (CDP) GROUP

The more severe, classic rhizomelic chondrodysplasia punctata type 1 can manifest in neonates with cataracts, rhizomelia, metaphyseal abnormalities, and punctate calcifications in the epiphyseal cartilage at the knee, hip, elbow, and shoulder, involving the hyoid bone, larynx, costochondral junctions, and vertebrae (chondrodysplasia punctata). In addition, unossified cartilage in the vertebral bodies show as radiolucent coronal clefts.

Figure 13. Rhizomelic chondrodysplasia punctate type 1. Punctate epitphyses, very small humeri less shortening of femurs, coronal clefts in vertebral bodies.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
CDP, X-linked dominant, Conradi-Hünermann type (CDPX2)	XLD	302960	55062	35173	*EBP*
CDP, X-linked recessive, brachytelephalangic type (CDPX1)	XLR	302950	1544	79345	*ARSE*
Congenital hemidysplasia, ichthyosis, limb defects (CHILD)	XLD	308050	51754	139	*NSDHL*
Congenital hemidysplasia, ichthyosis, limb defects (CHILD)	XLD	308050		139	*EBP*
Greenberg dysplasia	AR	215140		1426	*LBR*
Rhizomelic CDP type 1	AR	215100	1270	177	*PEX7*
Rhizomelic CDP type 2	AR	222765		177	*DHPAT*
Rhizomelic CDP type 3	AR	600121		177	*AGPS*
CDP tibial-metacarpal type	AD/AR	118651		79346	
Astley-Kendall dysplasia	AR?			85175	

Note that stippling can occur in several syndromes such as Zellweger, Smith-Lemli-Opitz and others. Please also refer to desmosterolosis as well as SEMD short limb—abnormal calcification type in group 11.

22. NEONATAL OSTEOSCLEROTIC DYSPLASIAS

Caffey disease manifests with subperiosteal new bone formation (long bones, ribs, mandible, scapulae, and clavicles) associated with fever, joint swelling and pain. Onset is around age two months and the episodes stop by age two years.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Blomstrand dysplasia	AR	215045		50945	*PTHR1*
Desmosterolosis	AR	602398		35107	*DHCR24*
Caffey disease (including infantile and attenuated forms)	AD	114000	99168	1310	*COL1A1*
Caffey disease (severe variants with prenatal onset)	AR	114000	99168	1310	*COL1A1*
Raine dysplasia (lethal and non-lethal forms)	AR	259775		1832	*FAM20C*

Please also refer to Astley-Kendall dysplasia and CDPs in group 21

23. INCREASED BONE DENSITY GROUP (WITHOUT MODIFICATION OF BONE SHAPE)

Osteopetrosis can manifest with increased bone density, diffuse and focal sclerosis, modelling defects at metaphyses, pathological fractures, osteomyelitis, tooth eruption defects and dental caries. Other

complications include cranial nerve compression, hydrocephalus, pancytopaenia, extramedullary haematopoiesis, hepatosplenomegaly, and hypocalcaemia (*10*).

Figure 14. Osteopetrosis. Thick dense bones, alternating bands of sclerosis and normal density bone in long bones, rugger jersey spine, dense base of skull.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Osteopetrosis, severe neonatal or infantile forms (OPTB1)	AR	259700		667	*TCIRG1*
Osteopetrosis, severe neonatal or infantile forms (OPTB4)	AR	611490	1127	667	*CLCN7*
Osteopetrosis, infantile form, with nervous system involvement (OPTB5)	AR	259720		667	*OSTM1*
Osteopetrosis, intermediate form, osteoclast-poor (OPTB2)	AR	259710		667	*TNFSF11*
Osteopetrosis, infantile form, osteoclast-poor with immunoglobulin deficiency (OPTB7)	AR	612301		667	*TNFRSF11A*
Osteopetrosis, intermediate form (OPTB6)	AR	611497		210110	*PLEKHM1*
Osteopetrosis, intermediate form (OPTA2)	AR	259710	1127	667	*CLCN7*
Osteopetrosis with renal tubular acidosis (OPTB3)	AR	259730		2785	*CA2*
Osteopetrosis, late-onset form type 1 (OPTA1)	AD	607634		2783	*LRP5*
Osteopetrosis, late-onset form type 2 (OPTA2)	AD	166600		53	*CLCN7*
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	XL	300301		69088	*IKBKG*
Osteopetrosis, moderate form with defective leucocyte adhesion (LAD3)	AR	612840		2968	*KIND3*
Pyknodysostosis	AR	265800		763	*CTSK*
Osteopoikilosis	AD	155950		2485	*LEMD3*
Melorheostosis with osteopoikilosis	AD	155950		2485	*LEMD3*
Osteopathia striata with cranial sclerosis (OSCS)	XLD	300373		2780	*WTX*
Melorheostosis	SP	155950		2485	*LEMD3*
Dysosteosclerosis	AR	224300		1782	*SLC29A3*
Osteomesopyknosis	AD	166450		2777	
Osteopetrosis with infantile neuroaxonal dysplasia	AR?	600329		85179	

24. INCREASED BONE DENSITY GROUP WITH METAPHYSEAL AND/OR DIAPHYSEAL INVOLVEMENT

Camurati-Engelmann manifests with bilateral cortical thickening (hyperostosis) of the diaphyses of the long bones starting with the femora and tibiae. The metaphyses and the skull base may be affected as well, but the epiphyses are spared. Limb pain, muscle weakness, a waddling gait, and easy fatigability can also occur.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Craniometaphyseal dysplasia, autosomal dominant type	AD	123000	1461	1522	*ANKH*
Diaphyseal dysplasia Camurati-Engelmann	AD	131300	1156	1328	*TGFB1*
Hematodiaphyseal dysplasia Ghosal	AR	231095		1802	*TBXAS1*
Hypertrophic osteoarthropathy	AR	259100		1525	*HPGD*
Pachydermoperiostosis (hypertrophic	AD	167100		2796	

osteoarthropathy, primary, autosomal dominant)					
Oculodentoosseous dysplasia (ODOD) mild type	AD	164200		2710	*GJA1*
Oculodentoosseous dysplasia (ODOD) severe type	AR	257850		2710	*GJA1*
Osteoectasia with hyperphosphatasia (juvenile Paget disease)	AR	239000		2801	*OPG*
Sclerosteosis	AR	269500	1228	3152	*SOST*
Endosteal hyperostosis, van Buchem type	AR	239100	1228	3416	*SOST*
Trichodentoosseous dysplasia	AD	190320		3352	*DLX3*
Craniometaphyseal dysplasia, autosomal recessive type	AR	218400		1522	*GJA1*
Diaphyseal medullary stenosis with bone malignancy	AD	112250		85182	*MTAP*
Craniodiaphyseal dysplasia	AD	122860	1228	1513	*SOST*
Craniometadiaphyseal dysplasia, Wormian bone type	AR	615118		85184	
Endosteal sclerosis with cerebellar hypoplasia	AR	213002		85186	
Lenz-Majewski hyperostotic dysplasia	SP	151050		2658	*PTDSS1*
Metaphyseal dysplasia, Braun-Tinschert type	XL	605946		85188	
Pyle disease	AR	265900		3005	*SFRP4*

25. OSTEOGENESIS IMPERFECTA AND DECREASED BONE DENSITY

Osteogenesis imperfect (OI) manifests with low bone mineral density and bone fragility with frequent fractures, bone deformities and short stature, dentinogenesis imperfecta (fragile grey or brown somewhat translucent teeth), and progressive hearing loss. In type I, stature is normal or slightly short, there is no bone deformity, the sclerae can be blue and there is no dentinogenesis imperfecta. Type II is the most severe with multiple rib and long bone fractures at or before birth, marked deformities, broad long bones, low density on skull X-rays, and dark sclera. OI type III presents with very short stature, a triangular face, severe scoliosis, gray sclera, and dentinogenesis imperfecta. In Type IV, the phenotype is milder with moderately short stature, mild to moderate scoliosis, grayish or white sclera, and dentinogenesis imperfecta. Type V is characterized by mild to moderate short stature, calcification of the forearm interosseous membrane, radial head dislocation and hyperplastic callus formation following fractures, and no dentinogenesis imperfecta.

Figure 15. OI type II. Wormian bones, thick short crumpled long bones, rectangular wavy femora, thick beaded ribs.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Osteogenesis imperfecta, non-deforming form (OI type I)	AD	166200	1295	216796	*COL1A1,COL1A2*
Osteogenesis imperfecta, perinatal lethal form (OI type II)	AD, AR	166210	1295	216804	*COL1A1,COL1A2,CRTAP,LEPRE1,PPIB*
Osteogenesis imperfecta, progressively deforming type (OI type III)	AD, AR	259420	1295	216812	*COL1A1,COL1A2,CRTAP,LEPRE1,PPIB,FKBP10,SERPINH1 , WNT1, TMEM38B*
Osteogenesis imperfecta, moderate form (OI type IV)	AD, AR	166220	1295	216820	*COL1A1,COL1A2,CRTAP,FKBP10,SP7*
Osteogenesis imperfecta with	AD	610967		216828	*IFITM5*

calcification of the interosseous membranes and/or hypertrophic callus (OI type V)					
Osteogenesis imperfecta, type VI	AR	613982		216812	*SERPINF1*
Osteogenesis imperfecta, type VII	AR	610682		216804	*CRTAP*
Bruck syndrome type 1 (BS1)	AR	259450		2771	*FKBP10*
Bruck syndrome type 2 (BS2)	AR	609220		2771	*PLOD2*
Osteoporosis-pseudoglioma syndrome	AR	259770		2788	*LRP5*
Calvarial doughnut lesions with bone fragility	AD	126550		85192	
Idiopathic juvenile osteoporosis	SP	259750		85193	
Cole-Carpenter dysplasia (bone fragility with craniosynostosis)	SP	112240		2050	*P4HB*
Spondylo-ocular dysplasia	AR	605822		85194	*XYLT2*
Osteopenia with radiolucent lesions of the mandible	AD	166260		53697	*ANO5*
Ehlers-Danlos syndrome, progeroid form	AR	130070		75496	*B4GALT7*
Geroderma osteodysplasticum	AR	231070		2078	*GORAB*
Cutis laxa, autosomal recessive form, type 2B (ARCL2B)	AR	612940		90350	*PYCR1*
Cutis laxa, autosomal recessive form, type 2A (ARCL2A) (Wrinkly skin syndrome)	AR	219200	5200	90350	*ATP6VOA2*
Wrinkly skin syndrome	AR	278250	5200	2834	*ATP6VOA2*
Singleton-Merten dysplasia	AD	182250		85191	*IFIH1*

26. ABNORMAL MINERALIZATION GROUP

Hypophosphatasia results from low alkaline phosphatase (TNSALP) activity. Inorganic pyrophosphate (PPi), an inhibitor of mineralization, and pyridoxal 5′-phosphate (PLP), are substrates that accumulate. The types include the prenatal benign form which spontaneously improves, perinatal (lethal), infantile (respiratory complications, premature craniosynostosis, widespread demineralization and rachitic changes in the metaphyses), childhood (skeletal deformities, short stature, and waddling gait), and adult (stress fractures, thigh pain, chondrocalcinosis and marked osteoarthropathy). Two other forms include odontohypophosphatasia (no clinical changes in long bones are present, only biochemical and dental manifestations such as premature exfoliation of fully rooted primary teeth and/or severe dental caries) and pseudohypophosphatasia (indistinguishable from infantile hypophosphatasia, but serum alkaline phosphatase activity is normal). Enzyme replacement is now available.

Hypophosphatemic rickets is discussed in detail in the section on bone and mineral metabolism of Endotext. Rickets manifests with bowing of the weight bearing bones. Other frequent manifestations are growth failure with disproportionate short stature, frontal bossing, and swelling of wrists, knees, and ankles. A rachitic rosary arises due to expansion of the costo-chondral junctions, and an inward diaphragmatic pull of soft rib cage leads to Harrison's sulcus (groove). Dentition may be delayed and enamel development can be impaired.

Figure 16. Rickets. Widened growth plates, cupping fraying of metaphyses, demineralization , widened anterior rib ends.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Hypophosphatasia, perinatal lethal and infantile forms	AR	241500	1150	436	*ALPL*
Hypophosphatasia, adult form	AD	146300	1150	436	*ALPL*
Hypophosphatemic rickets, X-linked dominant	XLD	307800	83985	89936	*PHEX*
Hypophosphatemic rickets, autosomal dominant	AD	193100		89937	*FGF23*
Hypophosphatemic rickets, autosomal recessive, type 1 (ARHR1)	AR	241520		289176	*DMP1*
Hypophosphatemic rickets, autosomal recessive, type 2 (ARHR2)	AR	613312		289176	*ENPP1*
Hypophosphatemic rickets with hypercalciuria, X-linked recessive	XLR	300554		1652	*ClCN5*
Hypophosphatemic rickets with hypercalciuria, autosomal recessive (HHRH)	AR	241530		157215	*SLC34A3*
Neonatal hyperparathyroidism, severe form	AR	239200		417	*CASR*
Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism	AD	145980		405	*CASR*
Calcium pyrophosphate deposition disease (familial chondrocalcinosis) type 2	AD	118600		1416	*ANKH*

27. LYSOSOMAL STORAGE DISEASES WITH SKELETAL INVOLVEMENT (DYSOSTOSIS MULTIPLEX GROUP).

Several lysosomal storage diseases manifest with dysostosis multiplex (*11*). Clinically, there is evolving joint contractures without inflammation. Radiologically, the skull shows an abnormal J-shaped sella turcica and a thickened diploic space. The ribs are oar-shaped ribs (widened anteriorly and tapered posteriorly) and clavicles are short and thickened. The spine shows multiple superiorly notched (inferiorly beaked) vertebrae and posterior scalloping. The pelvis shows rounded iliac wings and inferior tapering of the ilea. The long bones can have mildly hypoplastic epiphyses. The capital femoral epiphyses can be fragmented, and there can be proximal humeral notching, long and narrow femoral necks, hypoplastic distal ulnae, and thickened short diaphyses. In the hands, proximally pointed metacarpals are short and thick with thin cortices.

Figure 17. Mucopolysaccharidoses. Wide ribs, glenoid hypoplasia, steep acetabula with constricted iliac wings, flat/irregular femoral head , spearhead metacarpals, platyspondyly, central anterior vertebral body beaking, hypoplastic odontoid.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Mucopolysaccharidosis type 1H/1S	AR	607014	1162	93473	*IDUA*
Mucopolysaccharidosis type 2	XLR	309900	1274	580	*IDS*
Mucopolysaccharidosis type 3A	AR	252900		581	*SGSH*
Mucopolysaccharidosis type 3B	AR	252920		581	*NAGLU*
Mucopolysaccharidosis type 3C	AR	252930		581	*HSGNAT*
Mucopolysaccharidosis type 3D	AR	252940		581	*GNS*
Mucopolysaccharidosis type 4A	AR	253000	148668	582	*GALNS*
Mucopolysaccharidosis type 4B	AR	253010		582	*GLB1*
Mucopolysaccharidosis type 6	AR	253200		583	*ARSB*
Mucopolysaccharidosis type 7	AR	253220		584	*GUSB*
Fucosidosis	AR	230000		349	*FUCA1*
alpha-Mannosidosis	AR	248500	1396	61	*MAN2B1*

beta-Mannosidosis	AR	248510		118	*MANBA*
Aspartylglucosaminuria	AR	208400		93	*AGA*
GMI Gangliosidosis, several forms	AR	230500		354	*GLB1*
Sialidosis, several forms	AR	256550		812	*NEU1*
Sialic acid storage disease (SIASD)	AR	269920		834	*SLC17A5*
Galactosialidosis, several forms	AR	256540		351	*CTSA*
Multiple sulfatase deficiency	AR	272200		585	*SUMF1*
Mucolipidosis II (I-cell disease), alpha/beta type	AR	252500	1828	576	*GNPTAB*
Mucolipidosis III (Pseudo-Hurler polydystrophy), alpha/beta type	AR	252600	1875	577	*GNPTAB*
Mucolipidosis III (Pseudo-Hurler polydystrophy), gamma type	AR	252605	24701	577	*GNPTG*

28. OSTEOLYSIS GROUP

Hajdu-Cheney syndrome is characterized by short stature, bowing of the long bones, vertebral anomalies, progressive focal bone destruction, acroosteolysis and generalized osteoporosis. Facial features are coarse and can include hypertelorism, bushy eyebrows, micrognathia, a small mouth with dental anomalies, low-set ears, and short neck.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Familial expansile osteolysis	AD	174810		85195	*TNFRSF11A*
Mandibuloacral dysplasia type A	AD	248370		90153	*LMNA*
Mandibuloacral dysplasia type B	AR	608612		90154	*ZMPSTE24*
Progeria, Hutchinson-Gilford type	AD	176670	1121	740	*LMNA*
Torg-Winchester syndrome	AR	259600		3460	*MMP2*
Hajdu-Cheney syndrome	AD	102500		955	*NOTCH2*
Multicentric carpal-tarsal osteolysis with and without nephropathy	AD	166300		2774	*MAFB*
Lipomembraneous osteodystrophy with leukoencephalopathy (presenile dementia with bone cysts; Nasu-Hakola)	AR	221770	1197	2770	*TREM2*
Lipomembraneous osteodystrophy with leukoencephalopathy (presenile dementia with bone cysts; Nasu-Hakola)	AR	221770	1197	2770	*TYROBP*

Please also refer to Pycnodysostosis, cleidocranial dysplasia, and Singleton-Merten syndrome. Note: several neurologic conditions may cause acroosteolysis

29. DISORGANIZED DEVELOPMENT OF SKELETAL COMPONENTS GROUP

Multiple hereditary exostoses are characterized by projections of bone capped by cartilage, in the metaphyses and the diaphyses of long bones.

Fibrodysplasia ossificans progressiva (FOP) is characterized by malformation of the hallux during embryonic skeletal development and by progressive heterotopic endochondral ossification later in life. In the first decade, episodes of painful soft tissue swellings precipitated by soft tissue injury, intramuscular injections, viral infection, muscular stretching, falls or fatigue lead to heterotopic bone formation. The heterotopic bone forms in the skeletal muscles, tendons, ligaments, fascia, and

aponeuroses. This phenomenon is seen first in the dorsal, axial, cranial and proximal regions of the body, and later in the ventral, appendicular, caudal and distal regions.

Figure 18. Fibrodysplasia ossificans progressive. Trapezoid-shaped proximal phalanx of the great toe, soft tissue ossification, exostosis-like structures at sites of ligamentous attachment.

Fibrous dysplasia, polyostotic form, or McCune-Albright syndrome is characterized by polyostotic fibrous dysplasia, cafe au lait cutaneous spots and endocrinopathies (peripheral precocious puberty, thyroidopathies, acromegaly, etc.). The skeletal manifestations are asymmetric fibrous dysplasia affecting any bone. Pathologic fracture, pseudarthrosis, bone deformity such as the shepherd's crook of the proximal femurs are characteristic.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Multiple cartilaginous exostoses 1	AD	133700	1235	321	*EXT1*
Multiple cartilaginous exostoses 2	AD	133701	1235	321	*EXT2*
Multiple cartilaginous exostoses 3	AD	600209		321	
Cherubism	AD	118400	1137	184	*SH3BP2*
Fibrous dysplasia, polyostotic form, McCune-Albright syndrome	SP	174800		562	*GNAS*
Progressive osseous heteroplasia	AD	166350		2762	*GNAS*
Gnathodiaphyseal dysplasia	AD	166260		53697	*TMEM16E*
Metachondromatosis	AD	156250		2499	*PTPN11*
Osteoglophonic dysplasia	AD	166250	1455	2645	*FGFR1*
Fibrodysplasia ossificans progressiva (FOP)	AD, SP	135100		337	*ACVR1*
Neurofibromatosis type 1 (NF1)	AD	162200	1109	636	*NF1*
Carpotarsal osteochondromatosis	AD	127820		2767	
Cherubism with gingival fibromatosis (Ramon syndrome)	AR	266270		3019	
Dysplasia epiphysealis hemimelica (Trevor)	SP	127800		1822	
Enchondromatosis (Ollier)	SP	166000		296	*IDH1, IDH2, and PTH1R*
Enchondromatosis with hemangiomata (Maffucci)	SP	166000		296	*DH1, IDH2, and PTH1R*

Please also refer to Proteus syndrome in group 30.

30. OVERGROWTH SYNDROMES WITH SKELETAL INVOLVEMENT

Marfan syndrome manifests with skeletal, ocular and cardiovascular features. Skeletal features include joint laxity, scoliosis and extremities that are disproportionately long for the size of the trunk. Overgrowth of the ribs can cause pectus excavatum or carinatum. Ocular features include myopia and displacement of the lens from the center of the pupil. Cardiovascular features include dilatation of the aorta, susceptibility to aortic tear and rupture, mitral or tricuspid valve prolapse, and enlargement of the proximal pulmonary artery.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Weaver syndrome	SP/AD	277590		3447	*EZH2*
Sotos syndrome	AD	117550	1479	821	*NSD1*
Marshall-Smith syndrome	SP	602535		561	*NFIX*
Proteus syndrome	SP	176920	99495	744	*AKT1*

Marfan syndrome	AD	154700	1335	558	*FBN1*
Congenital contractural arachnodactyly	AD	121050	1386	115	*FBN2*
Loeys-Dietz syndrome types 1A and 2A	AD	609192,610168,	1133		*TGFBR1*
Loeys-Dietz syndrome types 1B and 2B	AD	608967, 610380	1133		*TGFBR2*
Loeys-Dietz syndrome, type 3	AD	613795	1133	284984	*SMAD3*
Loeys-Dietz syndrome, type 4	AD	614816	1133	91387	*TGFB2*
Overgrowth syndrome with 2q37 translocations	SP				*NPPC*
Overgrowth syndrome with skeletal dysplasia (Nishimura-Schmidt, endochondral gigantism)	SP?				

Please also refer to Shprintzen-Goldberg syndrome in Craniosynostosis group

31. GENETIC INFLAMMATORY/RHEUMATOID-LIKE OSTEOARTHROPATHIES

Familial hyperphosphatemic tumoral calcinosis is characterized by the progressive deposition of calcium phosphate crystals in periarticular spaces, soft tissues, and bones (periosteal reaction and cortical hyperostosis). It is caused by increased renal absorption of phosphate secondary to loss-of-function mutations in *FGF23* or *GALNT3*.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Progressive pseudorheumatoid dysplasia (PPRD; SED with progressive arthropathy)	AR	208230		1159	*WISP3*
Chronic infantile neurologic cutaneous articular syndrome (CINCA)/neonatal onset multisystem inflammatory disease (NOMID)	AD	607115		1451	*CIAS1*
Sterile multifocal osteomyelitis, periostitis, and pustulosis (CINCA/NOMID-like)	AR	612852		210115	*IL1RN*
Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anemia (CRMO with CDA; Majeed syndrome)	AR	609628	1974	77297	*LPIN2*
Tumoral calcinosis, hyperphosphatemic, familial	AR	211900		53715	*GALNT3, FGF23, KL*
Infantile systemic hyalinosis/Juvenile hyaline fibromatosis (ISH/JHF)	AR	236490	1525	2176	*ANTXR2*
camptodactyly-arthropathy-coxa vara-pericarditis syndrome (non-inflammatory)	AR	208250		2848	*PRG4*

32. CLEIDOCRANIAL DYSPLASIA AND ISOLATED CRANIAL OSSIFICATION DEFECTS GROUP

Cleidocranial dysplasia manifests with large, wide-open fontanels at birth which may remain open with bulging calvaria, mid-face hypoplasia, hypoplasia or aplasia of the clavicles permitting apposition of the shoulders, wide pubic symphysis, brachydactyly, tapering fingers, and short, broad thumbs, dental anomalies (delayed eruption of secondary dentition, failure to shed the primary teeth, supernumerary teeth with dental crowding, and malocclusion).

Figure 19. Cleidocranial dysplasia. Wormian bones, partial (or rarely complete) absence of clavicle, widened symphysis pubis, tall femoral head ossification centers, cone-shaped epiphyses.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Cleidocranial dysplasia	AD	119600	1513	1452	*RUNX2*
CDAGS syndrome (craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, genital anomalies, skin eruption)	AR	603116		85199	
Yunis-Varon syndrome	AR	216340		3472	*FIG4*
Parietal foramina (isolated)	AD	168500	1128	60015	*ALX4*
Parietal foramina (isolated)	AD	168500	1128	60015	*MSX2*

Please also refer to pycnodysostosis, wrinkly skin syndrome, and several others

33. CRANIOSYNOSTOSIS SYNDROMES

Craniosynostosis is often secondary to mutations in one of the FGFR genes (*12*). In Apert syndrome (FGFR2) there is midface hypoplasia and symmetrical syndactyly of hands and feet. In Crouzon syndrome there is maxillary hypoplasia, shallow orbits, ocular proptosis, and normal extremities. It is caused by FGFR2 mutations unless there is acanthosis nigricans (FGFR3). In Muenke syndrome (FGFR3), there is unilateral or bilateral coronal synostosis, and absent or minimal hand/foot anomalies. In Pfeiffer syndrome there is high forehead, maxillary hypoplasia, mild syndactyly of hands and/or feet, broad thumbs and/or great toe (FGFR2, rarely FGFR1). In Saethre-Chotzen syndrome there is brachycephaly/plagiocephaly, a high forehead, facial asymmetry, maxillary hypoplasia, brachydactyly, partial cutaneous syndactyly in some cases, and thumb/great toe anomalies (TWIST gene, occasionally FGFR3).

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Pfeiffer syndrome (FGFR1-related)	AD	101600	1455	710	*FGFR1*
Pfeiffer syndrome (FGFR2-related)	AD	101600	1455	710	*FGFR2*
Apert syndrome	AD	101200	1455	87	*FGFR2*
Craniosynostosis with cutis gyrata (Beare-Stevenson)	AD	123790	1455	1555	*FGFR2*
Crouzon syndrome	AD	123500	1455	207	*FGFR2*
Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome)	AD	612247	1455	93262	*FGFR3*
Craniosynostosis, Muenke type	AD	602849	1455	53271	*FGFR3*
Antley-Bixler syndrome	AR	201750	1419	63269	*POR*
Craniosynostosis Boston type	AD	604757		1541	*MSX2*
Saethre-Chotzen syndrome	AD	101400	1189	794	*TWIST1*
Shprintzen-Goldberg syndrome	AD	182212	1277	2462	*SKI*
Baller-Gerold syndrome	AR	218600	1204	1225	*RECQL4*
Carpenter syndrome	AR	201000		65759	*RAB23*

Please also refer to Cole-Carpenter syndrome in group 24, CDAGS syndrome in group 29, and Craniofrontonasal syndrome in group 34

34. DYSOSTOSES WITH PREDOMINANT CRANIOFACIAL INVOLVEMENT

Treacher Collins syndrome manifests with fdownslanting eyes, coloboma of the eyelids, micrognathia, microtia and other deformity of the ears, hypoplastic zygomatic arches, macrostomia, conductive hearing loss and cleft palate.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Mandibulo-facial dysostosis (Treacher Collins, Franceschetti-Klein)	AD	154500	1532	861	*TCOF1*
Mandibulo-facial dysostosis (Treacher-Collins, Franceschetti-Klein)	AD	154500	1532	861	*POLR1D*
Mandibulo-facial dysostosis (Treacher-Collins, Franceschetti-Klein)	AR	154500	1532	861	*POLR1C*
Oral-facial-digital syndrome type I (OFD1)	XLR	311200		2750	*CXORF5*
Weyer acrofacial (acrodental) dysostosis	AD	193530		952	*EVC1*
Endocrine-cerebro-osteodysplasia (ECO)	AR	612651		199332	*ICK*
Craniofrontonasal syndrome	XLD	304110		1520	*EFNB1*
Frontonasal dysplasia, type 1	AR	136760		250	*ALX3*
Frontonasal dysplasia, type 2	AR	613451		228390	*ALX4*
Frontonasal dysplasia, type 3	AR	613456		306542	*ALX1*
Hemifacial microsomia	SP/AD	164210	5199	374	
Miller syndrome (postaxial acrofacial dysostosis)	AR	263750		246	*DHODH*
Acrofacial dysostosis, Nager type	AD/AR	154400		245	*SF3B4*
Acrofacial dysostosis, Rodriguez type	AR	201170		1788	

Please also refer to Oral-facial-digital syndrome type IV in the Short Rib Dysplasias group

35. DYSOSTOSES WITH PREDOMINANT VERTEBRAL WITH AND WITHOUT COSTAL INVOLVEMENT

In spondylocostal dysostosis, there are multiple segmentation defects of the vertebrae, malalignment of the ribs with variable points of intercostal fusion, and a reduction in rib number. Clinically there is scoliosis, a short neck and trunk.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Currarino triad	AD	176450		1552	*HLXB9*
Spondylocostal dysostosis type 1 (SCD1)	AR	277300	8828	2311	*DLL3*
Spondylocostal dysostosis type 2 (SCD2)	AR	608681	8828	2311	*MESP2*
Spondylocostal dysostosis type 3 (SCD3)	AR?	609813	8828	2311	*LFNG*
Spondylocostal dysostosis type 4 (SCD4)	AR	613686	8828	2311	*HES7*
Spondylothoracic dysostosis	AR	122600	8828	1797	*MESP2*
Klippel-Feil anomaly with laryngeal malformation	AD	118100		2345	*GDF6*
Spondylocostal/thoracic dysostosis, other forms	AD/AR				
Cerebro-costo-mandibular syndrome (rib gap syndrome)	AD/AR	117650		1393	*SNRPB*
Cerebro-costo-mandibular-like syndrome with vertebral defects	AR	611209		263508	*COG1*

Diaphanospondylodysostosis	AR	608022		66637	*BMPER*

Please also refer to Spondylocarpotarsal dysplasia in group 7 and spondylo-metaphyseal-megaepiphyseal dysplasia in group 13

36. PATELLAR DYSOSTOSES

Nail-patella syndrome presents with patella hypoplasia, nail hypoplasia or dystrophy, elbow and knee deformities (limitation of elbow extension, pronation, and supination; cubitus valgus; and antecubital pterygia), iliac horns (bilateral, conical bony processes projecting posteriorly and laterally from the central part of the iliac bones of the pelvis), nephropathy (nephrotic syndrome which may progress to end-stage renal disease), and ocular defects (cloverleaf appearance of the iris, primary open angle glaucoma).

Figure 20. Nail-patella syndrome. Absent patella, iliac horns, radial head dislocation, spondylolysthesis.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Ischiopatellar dysplasia (small patella syndrome)	AD	147891		1509	*TBX4*
Small patella—like syndrome with clubfoot	AD	119800		293150	*PITX1*
Nail-patella syndrome	AD	161200	1132	2614	*LMX1B*
Genitopatellar syndrome	AR?	606170	114806	85201	*KAT6B*
Ear-patella-short stature syndrome (Meier-Gorlin)	AR	224690		2554	*ORC1, ORC1L, ORC4, ORC4L, ORC6, ORC6L, CDT1, CDC6, CDC18L*

Please also refer to MED group for conditions with patellar changes as well as ischio-pubic-patellar dysplasia as mild expression of campomelic dysplasia

37. BRACHYDACTYLIES (WITH OR WITHOUT EXTRASKELETAL MANIFESTATIONS)

Coffin-Siris syndrome (CSS) is characterized by aplasia or hypoplasia of the distal phalanx or nail of the fifth digit (or more digits), distinctive facial features (wide mouth with thick, everted upper and lower lips, broad nasal bridge with broad nasal tip, thick eyebrows and long eyelashes), and moderate to severe developmental/cognitive delay.

Thorough discourses on the genes involved in each condition can be found in papers by Schwabe and Mundlos (*13*), Temtamy and Aglan (*14*), and Mundlos (*15*).

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Brachydactyly type A1	AD	112500		93388	*IHH*
Brachydactyly type A1	AD				*5p13.3-p13.2*
Brachydactyly type A2	AD	112600		93396	*BMPR1B*
Brachydactyly type A2	AD	112600		93396	*BMP2*
Brachydactyly type A2	AD	112600		93396	*GDF5*
Brachydactyly type A3	AD	112700		93393	
Brachydactyly type B	AD	113000		93383	*ROR2*
Brachydactyly type B2	AD	611377		140908	*NOG*
Brachydactyly type C	AD, AR	113100		93384	*GDF5*

Brachydactyly type D	AD	113200		93385	*HOXD13*
Brachydactyly type E	AD	113300		93387	*PTHLH*
Brachydactyly type E	AD	113300		93387	*HOXD13*
Brachydactyly—mental retardation syndrome	AD	600430		1001	*HDAC4*
Hyperphosphatasia with mental retardation, brachytelephalangy, and distinct face	AR	239300		247262	*PIGV*
Brachydactyly-hypertension syndrome (Bilginturian)	AD	112410		1276	
Brachydactyly with anonychia (Cooks syndrome)	AD	106995		1487	*SOX9*
Microcephaly-oculo-digito-esophageal-duodenal syndrome (Feingold syndrome)	AD	164280	7050	1305	*MYCN*
Hand-foot-genital syndrome	AD	140000	1423	2438	*HOXA13*
Brachydactyly with elbow dysplasia (Liebenberg syndrome)	AD	186550		1275	*PITX1*
Keutel syndrome	AR	245150		85202	*MGP*
Albright hereditary osteodystrophy (AHO)	AD	103580		665	*GNAS1*
Rubinstein-Taybi syndrome	AD	180849	1526	783	*CREBBP*
Rubinstein-Taybi syndrome	AD	180849	1526	783	*EP300*
Catel-Manzke syndrome	XLR?	302380		1388	
Brachydactyly, Temtamy type	AR	605282			*CHSY1*
Christian type brachydactyly	AD	112450		1278	
Coffin-Siris syndrome	AR	135900	131811	1465	*SMARCA2, SMARCA4, SMARCB1, SMARCE1, ARID1A, ARID1B*
Mononen type brachydactyly	XLD?	301940		2565	
Poland anomaly	SP	173800		2911	

Please also refer to group 20 for other conditions with brachydactyly as well as brachytelephalangic CDP

38. LIMB HYPOPLASIA—REDUCTION DEFECTS GROUP

Fanconi anemia can present with bone marrow failure, developmental delay and central nervous system malformation, short stature, skeletal anomalies often involving the radial ray, anomalies of the eyes, kidneys and urinary tract, ears (including deafness), heart, gastrointestinal system, abnormal skin pigmentation, and hypogonadism. There is an increased risk of malignancy.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Ulnar-mammary syndrome	AD	181450		3138	*TBX3*
de Lange syndrome	AD	122470	1104	199	*NIPBL*
Fanconi anemia	AR	227650	1401	84	*Several genes, see OMIM*

Thrombocytopenia-absent radius (TAR)	AR?/AD?	274000	23758	3320	*Several*
Thrombocythemia with distal limb defects	AD			329319	*THPO*
Holt-Oram syndrome	AD	142900	1111	392	*TBX5*
Okihiro syndrome (Duane—radial ray anomaly)	AD	607323	1373	959	*SALL4*
Cousin syndrome	AR	260660		93333	*TBX15*
Roberts syndrome	AR	268300	1153	3103	*ESCO2*
Split-hand-foot malformation with long bone deficiency (SHFLD1)	AD	119100		3329	
Split-hand-foot malformation with long bone deficiency (SHFLD2)	AD	610685		3329	
Split-hand-foot malformation with long bone deficiency (SHFLD3)	AD	612576		3329	
Tibial hemimelia	AR	275220		93322	
Tibial hemimelia-polysyndactyly-triphalangeal thumb	AD	188770		3332	
Acheiropodia	AR	200500		931	*LMBR1*
Tetra-amelia	XL	301090	1276	3301	
Tetra-amelia	AR	273395	1276	3301	*WNT3*
Ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC)	AD	106260	43797	1071	*TP63*
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome Type 3 (EEC3)	AD	604292		1896	*TP63*
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 1 (EEC1)	AD	129900		1896	
Ectrodactyly-ectodermal dysplasia-macular dystrophy syndrome (EEM)	AR	225280		1897	*CDH3*
Limb-mammary syndrome (including ADULT syndrome)	AD	603543	43797	69085	*TP63*
Split hand-foot malformation, isolated form, type 4 (SHFM4)	AD	605289	43797	2440	*TP63*
Split hand-foot malformation, isolated form, type 1 (SHFM1)	AD	183600		2440	
Split hand-foot Malformation, isolated form, type 2 (SHFM2)	XL	313350		2440	
Split hand-foot malformation, isolated form, type 3 (SHFM3)	AD	246560		1307	*FBXW4*
Split hand-foot malformation, isolated form, type 5 (SHFM5)	AD	606708		2440	
Split-hand/foot malformation 1 with sensorineural hearing loss	AR	220600		71271	*DLX5*
Split-hand/foot malformation 6	AR	225300		2440	*WNT10B*
Al-Awadi Raas-Rothschild limb-pelvis hypoplasia-aplasia	AR	276820		2879	*WNT7A*
Fuhrmann syndrome	AR	228930		2854	*WNT7A*
RAPADILINO syndrome	AR	266280	1204	3021	*RECQL4*
Adams-Oliver syndrome	AD/AR	100300		974	*ARHGAP31, DOCK6, RBPJ,*

					EOGT
Femoral hypoplasia-unusual face syndrome (FHUFS)	SP/AD?	134780		1988	
Femur-fibula-ulna syndrome (FFU)	SP?	228200		2019	
Hanhart syndrome (hypoglossia-hypodactylia)	AD	103300		989	
Scapulo-iliac dysplasia (Kosenow)	AD	169550		2839	

Please also refer to CHILD in group 20 and the mesomelic and acromesomelic dysplasias

39. POLYDACTYLY-SYNDACTYLY-TRIPHALANGISM GROUP

Pallister-Hall syndrome manifests with hypothalamic hamartoma, pituitary dysfunction, bifid epiglottis, laryngotracheal cleft, central polydactyly, and visceral malformations.

Meckel syndrome presents with variable combinations of renal cysts, developmental anomalies of the central nervous system (occipital encephalocele), hepatic ductal dysplasia and cysts, and polydactyly.

Group/name of disorder	Inher.	OMIM	GR	Orpha	Gene
Preaxial polydactyly type 1 (PPD1)	AD	174400		93339	*SHH*
Preaxial polydactyly type 1 (PPD1)	AD	174400		93339	*Other locus*
Preaxial polydactyly type 2 (PPD2)/triphalangeal thumb (TPT)	AD	174500		2950	*SHH*
Preaxial polydactyly type 3 (PPD3)	AD	174600		93337	*Other locus*
Preaxial polydactyly type 4 (PPD4)	AD	174700		93338	*GLI3*
Greig cephalopolysyndactyly syndrome	AD	175700	1446	380	*GLI3*
Pallister-Hall syndrome	AD	146510	1465	672	*GLI3*
Synpolydactyly (complex, fibulin1—associated)	AD	608180		295197	*FBLN1*
Synpolydactyly	AD	186000		295195	*HOXD13*
Townes-Brocks syndrome (Renal-Ear-Anal-Radial syndrome)	AD	107480	1445	857	*SALL1*
Lacrimo-auriculo-dento-digital syndrome (LADD)	AD	149730		2363	*FGFR2, FGFR3, FGF10*
Acrocallosal syndrome	AR	200990		36	*KIF7*
Acro-pectoral syndrome	AD	605967		85203	
Acro-pectoro-vertebral dysplasia (F-syndrome)	AD	102510		957	
Mirror-image polydactyly of hands and feet (Laurin-Sandrow syndrome)	AD	135750		2378	*SHH*
Mirror-image polydactyly of hands and feet (Laurin-Sandrow syndrome)					*Other locus*
Cenani-Lenz syndactyly	AR	212780		3258	*LRP4*
Cenani-Lenz like syndactyly	SP (AD?)				*GREM1, FMN1*
Oligosyndactyly, radio-ulnar synostosis, hearing loss, and renal defects syndrome	SP (AR?)				*FMN1*
Syndactyly, Malik-Percin type	AR	609432		157801	*BHLHA9*
STAR syndrome (syndactyly of toes, telecanthus, ano-, and renal	XL	300707		140952	*FAM58A*

malformations)					
Syndactyly type 1 (III-IV)	AD	185900		93402	
Syndactyly type 3 (IV-V)	AD	185900		93402	*GJA1*
Syndactyly type 4 (I-V) Haas type	AD	186200		93405	*SHH*
Syndactyly type 5 (syndactyly with metacarpal and metatarsal fusion)	AD	186300		93406	*HOXD13*
Syndactyly with craniosynostosis (Philadelphia type)	AD	601222		1527	
Syndactyly with microcephaly and mental retardation (Filippi syndrome)	AR	272440		3255	*CKAP2L*
Jawad syndrome	AR	251255		313795	*RBBP8*
Meckel syndrome type 1	AR	249000		564	*MKS1*
Meckel syndrome type 2	AR	603194		564	*TMEM216*
Meckel syndrome type 3	AR	607361		564	*TMEM67*
Meckel syndrome type 4	AR	611134		564	*CEP290*
Meckel syndrome type 5	AR	611561		564	*RPGRIP1L*
Meckel syndrome type 6	AR	612284		564	*CC2D2A*

Note: the Smith-Lemli-Opitz syndrome can present with polydactyly and/or syndactyly. Please also refer to the SRPS group.

40. DEFECTS IN JOINT FORMATION AND SYNOSTOSES

Proximal symphalangism is characterized by fusion of the proximal interphalangeal joints, but can also involve the elbows, ankles and wrists leading to ankylosis. Conductive deafness secondary to fusion of the ossicles is also seen.

Group/name of disorder	Inher.	OMIM	Orpha	Gene
Multiple synostoses syndrome type 1	AD	186500	3237	*NOG*
Multiple synostoses syndrome type 2	AD	186500	3237	*GDF5*
Multiple synostoses syndrome type 3	AD	612961	3237	*FGF9*
Proximal symphalangism type 1	AD	185800	3250	*NOG*
Proximal symphalangism type 2	AD	185800	3250	*GDF5*
Radio-ulnar synostosis with amegakaryocytic thrombocytopenia	AD	605432	71289	*HOXA11*

Please also refer to Spondylo-Carpal-Tarsal dysplasia; mesomelic dysplasia with acral synostoses; and others.

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