Received: 16 August 2019 | Revised: 1 September 2019 | Accepted: 5 September 2019

DOI: 10.1002/ajmg.a.61366

AMERICAN JOURNAL OF medical genetics PART A WILEY

ORIGINAL ARTICLE

Nosology and classification of genetic skeletal disorders: 2019 revision

Geert R. Mortier[1] | Daniel H. Cohn[2] | Valerie Cormier-Daire[3] | Christine Hall[4] | Deborah Krakow[5] | Stefan Mundlos[6] | Gen Nishimura[7] | Stephen Robertson[8] | Luca Sangiorgi[9] | Ravi Savarirayan[10] | David Sillence[11] | Andrea Superti-Furga[12] | Sheila Unger[12] | Matthew L. Warman[13]

[1]Department of Medical Genetics, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

[2]Department of Molecular, Cell and Developmental Biology and Department of Orthopaedic Surgery, University of California at Los Angeles, Los Angeles, California

[3]IMAGINE Institute, Hôpital Necker Enfants Malades, Paris, France

[4]Department of Radiology, Great Ormond Street Hospital, London, UK

[5]Department of Obstetrics and Gynecology and Department of Orthopaedic Surgery and Human Genetics, University of California at Los Angeles, Los Angeles, California

[6]Institute for Medical Genetics and Human Genetics, Charité Universitätsmedizin Berlin, Berlin, Germany

[7]Department of Radiology, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

[8]Department of Paediatrics and Child Health, Dunedin School of Medicine, Otago University, Dunedin, New Zealand

[9]Department of Medical Genetics and Skeletal Rare Diseases, IRCCS Rizzoli Orthopaedic Institute, Bologna, Italy

[10]Murdoch Childrens Research Institute and University of Melbourne, Parkville, Victoria, Australia

[11]Discipline of Genomic Medicine, the Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

[12]Medical Genetics Service, CHUV, University of Lausanne, Lausanne, Switzerland

[13]Orthopaedic Research Laboratories, Boston Children's Hospital, Boston, Massachusetts

Correspondence
Geert Mortier, MD, PhD, Department of Medical Genetics, Antwerp University Hospital and University of Antwerp, Prins Boudewijnlaan, 43/6, Antwerp (Edegem) B-2650, Belgium.
Email: geert.mortier@uantwerpen.be

Abstract

The application of massively parallel sequencing technology to the field of skeletal disorders has boosted the discovery of the underlying genetic defect for many of these diseases. It has also resulted in the delineation of new clinical entities and the identification of genes and pathways that had not previously been associated with skeletal disorders. These rapid advances have prompted the Nosology Committee of the International Skeletal Dysplasia Society to revise and update the last (2015) version of the Nosology and Classification of Genetic Skeletal Disorders. This newest and tenth version of the Nosology comprises 461 different diseases that are classified into 42 groups based on their clinical, radiographic, and/or molecular phenotypes. Remarkably, pathogenic variants affecting 437 different genes have been found in 425/461 (92%) of these disorders. By providing a reference list of recognized entities and their causal genes, the Nosology should help clinicians achieve accurate diagnoses for their patients and help scientists advance research in skeletal biology.

KEYWORDS

dysostoses, Nosology, skeletal dysplasias, skeletal genetics, skeletal malformation syndromes

1 | INTRODUCTION

Fifty years ago, in 1969, an international team of experts in radiology, orthopedic surgery, pediatrics, and genetics convened in Paris to develop an International Nomenclature of Constitutional Diseases of Bones (A Nomenclature for Constitutional (Intrinsic) Diseases of Bones, 1971; International Nomenclature of Constitutional Diseases of Bones, 1970; International Nomenclature of Constitutional Bone Diseases, 1971; McKusick & Scott, 1971). The goal was to reach an agreement on the nomenclature of several genetic skeletal disorders that were reported since the early 1960s. At that time, there was growing evidence that genetic skeletal disorders were more heterogeneous than previously thought. The medical community started to appreciate the clinical and radiographic diversity among individuals with a "constitutional" bone disorder. It had become clear that not all individuals with short limbs had achondroplasia and that not all individuals with a short trunk had Morquio syndrome. The rapid progress in the delineation of new entities prompted the group to update the Nomenclature on several occasions, with revisions in 1977, 1983, 1992, and 1997 (International Nomenclature of Constitutional Diseases of Bones, 1979, 1983; International Nomenclature and Classification of the Osteochondrodysplasias, 1998; Beighton et al., 1992; Lachman, 1998; Rimoin, 1997; Spranger, 1992). After the establishment of the International Skeletal Dysplasia Society (ISDS) in 1999, revisions of the Nomenclature (Nosology) were delegated to an expert committee nominated within the ISDS and representing a good mix of clinical, radiological, and genetics expertise. The first ISDS revision was published in 2002 and thereafter at regular intervals (Bonafe et al., 2015; Hall, 2002; Superti-Furga & Unger, 2007; Warman et al., 2011). Here, we provide the 2019 revision and 10th edition of the Nosology and Classification of Genetic Skeletal Disorders.

2 | METHODOLOGY

The preparation of this paper started in September 2017, when members of the ISDS Nosology Committee met in Bruges, just before the 13th biannual ISDS meeting (September 20–23, 2017). Participants were: D. Cohn, V. Cormier-Daire, C. Hall, G. Mortier (chair), G. Nishimura, L. Sangiorgi, R. Savarirayan, D. Sillence, A. Superti-Furga, S. Unger, and M. Warman. The goal was to revise and update the last (2015) edition of the Nosology. Prior to this meeting, two to three curators were appointed for each group of disorders listed in the 2015 revision paper. Each member was assigned to one or more groups as the following: DC to groups 2, 3, 6, 7, 8, and 10; VCD to groups 1, 9, 15, 20, and 30; CH to groups 23, 24, 32, 33, and 36; DK to groups 7 and 9; GM to groups 2, 3, 10, 16, 28, 30, and 35; SM to groups 37–42; GN to groups 13, 18, 19, 21, 26, 28, 34, and 36; SR to group 7; LS to groups 25 and 29; RS to groups 1, 17, 19, and 33; DS to groups 22–27; ASF to groups 4, 11, 12, 20, 31, and 35; SU to groups 5, 8, 10, 14, and 22 and MW to groups 3, 16, and 29. They were responsible for reviewing the available literature and suggesting possible changes ahead of the meeting. During the meeting, the proposals by different curators were discussed and a consensus was reached on the general approach and methodology for the revision. After the meeting, drafts were circulated and continuously updated until August 4, 2019, which finally resulted in the current version.

The criteria used for inclusion of individual disorders were essentially unchanged from previous revisions and included the following: (a) the disorder should have significant skeletal involvement, corresponding to the definition of either skeletal dysplasias/dysostoses, metabolic bone disorders, or skeletal malformation/reduction syndromes; (b) the disorder should have achieved peer-reviewed publication status with listing in PubMed, OMIM, or another biomedical archive/database; (c) the disorder should have a genetic basis proven by pedigree or by occurrence of the same phenotype in unrelated families or by molecular analysis (mutation or linkage analysis); (d) the disorder should have nosologic autonomy; that is, it should represent an independent entity and not just a variation of an already existing entity. Each disorder that met these criteria received a separate listing as one entry regardless of the inheritance pattern or causal gene(s), unless there was evidence that the disorder encompassed phenotypically different conditions. For example, omodysplasia (group 17) is listed as two separate entities, because there is an important phenotypic difference between the autosomal dominant and autosomal recessive types, which is exemplified by their different genetic cause. On the other hand, the perinatally lethal form of osteogenesis imperfecta (OI type 2) (group 25) only receives one entry despite the different involved genes and inheritance patterns. In contrast to the previous revisions, it was decided not to list the protein anymore, since this information can be easily deduced from the gene. Gene symbols used were those approved by the HUGO Gene Nomenclature Committee. In addition to the OMIM number, the ORPHANET code (where available) was also listed for each disorder. Although some disorders could be classified into different groups, the committee chose to list each disorder only once to avoid redundancy in the Nosology.

3 | RESULTS

The updated Nosology comprises 461 disorders classified within 42 different groups (Table 1). The overall number of groups remains unchanged in comparison to the previous (2015) revision but two groups have changed names. Group 18 is now the "Bent bone dysplasia group" instead of "Campomelic dysplasia and related disorders," hereby referring to the common radiographic sign of bent bones in these disorders. Group 19 changed from "Slender bone dysplasia group" to "Primordial dwarfism and slender bones group." Genomic alterations affecting 437 different genes have been found in 425 of the listed disorders. Pathogenic variants in one gene can cause several phenotypes (e.g., groups 1, 2, 5, 6, and 8) and one phenotype can be caused by variants in several genes (e.g., groups 9 and 25). Pathogenic variants in *FGFR3*, *COL2A1*, *COMP*, *NPR2*, and *ACAN* can cause mild phenotypes such as isolated short stature or premature degenerative joint disease.

TABLE 1 List of the 461 skeletal disorders classified into 42 groups. For each disorder, the inheritance pattern and causal gene (if known) are shown. Locus heterogeneity is represented by a separate line per disorder. Where available, one or more OMIM numbers and ORPHANET codes are shown for each disorder. With respect to the Inheritance column, the symbol "SP" refers to somatic mosaicism resulting in sporadic occurrence (due to postzygotic genetic alterations). It is not used for those conditions that are caused by germline pathogenic variants but in whom sporadic occurrence is often observed because of early lethality or reduced reproductive fitness. Since the distinction between recessive and dominant inheritance for X-linked disorders is often artificial, the Nosology Committee elected to list these disorders only as "XL". [Color table can be viewed at wileyonlinelibrary.com]

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
1. FGFR3 chondrodysplasia group					
Thanatophoric dysplasia type 1	AD	*FGFR3*	187600	18060	Includes previous San Diego type
Thanatophoric dysplasia type 2	AD	*FGFR3*	187601	93274	
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	AD	*FGFR3*	616482	85165	
Achondroplasia	AD	*FGFR3*	100800	15	
Hypochondroplasia	AD	*FGFR3*	146000	427	
Camptodactyly, tall stature and hearing loss syndrome (CATSHL)	AD, AR	*FGFR3*	610474	85164	Loss-of-function mutations
See also group 33 for craniosynostosis syndromes linked to *FGFR3* mutations, as well as LADD syndrome in group 41 for another *FGFR3*-related phenotype					
2. Type 2 collagen group					
Achondrogenesis type 2 (Langer–Saldino)	AD	*COL2A1*	200610	93296	Achondrogenesis type 2 and hypochondrogenesis form one phenotypic continuum
Hypochondrogenesis	AD	*COL2A1*	200610	93297	Achondrogenesis type 2 and hypochondrogenesis form one phenotypic continuum
Platyspondylic dysplasia, Torrance type	AD	*COL2A1*	151210	85166	See also severe spondylodysplastic dysplasias (group 14)
Spondyloepiphyseal dysplasia congenita (SEDC)	AD, AR*	*COL2A1*	183900 616583 604864	94068	Includes mild skeletal dysplasia (SED) with premature onset arthrosis and SED Stanescu type. Mild SED cases may resemble multiple epiphyseal dysplasia (MED) (see note). AR*: A few cases with biallelic COL2A1 mutations have been reported
Spondyloepiphyseal dysplasia with marked metaphyseal changes (SEMD)	AD	*COL2A1*	184250 184253 184255	93346 93316 93315 85198	Includes SEMD Strudwick type, SMD Algerian type, dysspondyloenchondromatosis and some cases of SMD corner fracture type
Kniest dysplasia	AD	*COL2A1*	156550	485	
Spondyloperipheral dysplasia	AD	*COL2A1*	271700	1856	
SED with metatarsal shortening (formerly Czech dysplasia)	AD	*COL2A1*	609162	137678	Often associated with the p.R275C mutation
Stickler syndrome type 1	AD	*COL2A1*	108300	828 90653	See also *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3*
Dysplasia of the proximal femoral epiphyses	AD	*COL2A1*	608805 150600	2380	Heterogeneous condition, not all cases are due to *COL2A1* mutations (usually p.G393S; p.G717S; p.G1170S)
See also group 10 (multiple epiphyseal dysplasia) for overlapping phenotypes with normal stature and premature onset arthrosis					

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
3. Type 11 collagen group					
Stickler syndrome type 2	AD	*COL11A1*	604841	90654	Can also result from somatic mosaicism for a *COL11A1* mutation
Marshall syndrome	AD	*COL11A1*	154780	560	One report with homozygous p.Gly901Glu mutation in two affected sibs (PMID 22499343)
Stickler syndrome type 3 (nonocular)	AD	*COL11A2*	184840	166100	
Fibrochondrogenesis	AR, AD AR, AD	*COL11A1* *COL11A2*	228520 614524	2021	
Otospondylomegaepiphyseal dysplasia (OSMED), recessive type	AR	*COL11A2*	215150	1427	
Otospondylomegaepiphyseal dysplasia (OSMED), dominant type (Weissenbacher–Zweymüller syndrome, Stickler syndrome type 3)	AD	*COL11A2*	184840	3450	
See also Stickler syndrome type 1 in group 2					
4. Sulphation disorders group					
Achondrogenesis type 1B (ACG1B)	AR	*SLC26A2*	600972	93298	Formerly known as achondrogenesis, Fraccaro type
Atelosteogenesis type 2 (AO2)	AR	*SLC26A2*	256050	56304	Includes de la Chapelle dysplasia, McAlister dysplasia, and neonatal osseous dysplasia
Diastrophic dysplasia (DTD)	AR	*SLC26A2*	222600	628	
MED, autosomal recessive type	AR	*SLC26A2*	226900	93307	Classified in OMIM as EDM4; see also multiple epiphyseal dysplasia and pseudoachondroplasia group (group 10) and EDM7 in group 20
SEMD, PAPSS2 type	AR	*PAPSS2*	612847	93282	Formerly "Pakistani type." See also SEMD group (group 13)
Brachyolmia, recessive type	AR	*PAPSS2*	612847	448242	Probably includes Toledo and Hobaek types of brachyolmia
Chondrodysplasia gPAPP type (includes Catel–Manzke-like syndrome)	AR	*IMPAD1*	614078	280586	
Chondrodysplasia with congenital joint dislocations, CHST3 type (recessive Larsen syndrome)	AR	*CHST3*	143095	263463	Includes recessive Larsen syndrome, humero-spinal dysostosis, and SED Omani type
Ehlers–Danlos syndrome, musculocontractural type	AR AR	*CHST14* *DSE*	601776 615539	2953	Includes adducted thumb-clubfoot syndrome
See also group 7 and group 20 for other conditions with multiple dislocations.					
5. Perlecan group					
Dyssegmental dysplasia, Silverman–Handmaker and Rolland–Desbuquois types	AR	*HSPG2*	224410 224400	1865 156731	
Schwartz–Jampel syndrome (myotonic chondrodystrophy)	AR	*HSPG2*	255800	800	Mild and severe forms; includes previous Burton dysplasia
Note: *HSPG2* encodes perlecan, hence the group name					
6. Aggrecan group					
SED, Kimberley type	AD	*ACAN*	608361	253	
SEMD, Aggrecan type	AR	*ACAN*	612813	171866	
Short stature and advanced bone age	AD	*ACAN*	165800	364817	Sometimes with osteochondritis dissecans

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
7. Filamin group and related disorders					
Frontometaphyseal dysplasia	XL AD AD	*FLNA* *MAP3K7* *TAB2*	305620 617137	1826	
Cardiospondylocarpofacial syndrome	AD	*MAP3K7*	157800	3238	
Melnick–Needles syndrome	XL	*FLNA*	309350	2484	Includes osteodysplasty
Otopalatodigital syndrome type 1 (OPD1)	XL	*FLNA*	311300	90650	
Otopalatodigital syndrome type 2 (OPD2)	XL	*FLNA*	304120	90650	
Terminal osseous dysplasia (TOD)	XL	*FLNA*	300244	88630	Includes digitocutaneous dysplasia
Atelosteogenesis type 1 (AO1)	AD	*FLNB*	108720 112310	1190 1263	Includes Boomerang dysplasia, Piepkorn dysplasia, and spondylohumerofemoral (giant cell) dysplasia
Atelosteogenesis type 3 (AO3)	AD	*FLNB*	108721	56305	
Larsen syndrome (dominant)	AD	*FLNB*	150250	503	
Spondylocarpotarsal synostosis syndrome	AR AD, AR	*FLNB* *MYH3*	272460	3275	
Frank-ter Haar syndrome	AR	*SH3PXD2B*	249420	137834	Includes Borrone dermatocardioskeletal syndrome
See also group 4 for recessive Larsen syndrome and group 20 for conditions with multiple dislocations					
8. TRPV4 group					
Metatropic dysplasia	AD	*TRPV4*	156530	2635	Includes "hyperplastic," lethal and nonlethal forms. Can also result from somatic mosaicism for a *TRPV4* mutation
Spondyloepimetaphyseal dysplasia, Maroteaux type (pseudo-Morquio syndrome type 2)	AD	*TRPV4*	184095	263482	Includes parastremmatic dwarfism (OMIM 168400)
Spondylometaphyseal dysplasia, Kozlowski type	AD	*TRPV4*	184252	93314	
Brachyolmia, autosomal dominant type	AD	*TRPV4*	113500	93304	
Familial digital arthropathy with brachydactyly	AD	*TRPV4*	606835	85169	
See also groups 4 and 13 for other forms of brachyolmia					
9. Ciliopathies with major skeletal involvement					
Chondroectodermal dysplasia (Ellis-van Creveld)	AR AR AR AR	*EVC1* *EVC2* *WDR35* *DYNC2LI1*	225500	289	See also Weyers acrofacial (acrodental) dysostosis in group 34
Short rib–polydactyly syndrome (SRPS) type 1/3 (Saldino–Noonan/Verma–Naumoff)	AR AR AR AR AR	*DYNC2H1* *IFT80* *WDR34* *WDR60* *DYNC2LI1*	613091	93270 93271	There is significant clinical and radiological overlap between SRP1/3 and ATD. Some forms of both remain unlinked to the known genes.
Asphyxiating thoracic dysplasia (ATD; Jeune)	AR AR AR AR AR AR AR	*DYNC2H1* *DYNC2LI1* *WDR34* *TCTEX1D2* *WDR60* *WDR19* *IFT140*	613091	474	Dynein motor Retrograde transport (IFT-A)

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
	AR	*TTC21B*			
	AR	*IFT80*			Anterograde transport (IFT-B)
	AR	*IFT172*			
	AR	*IFT81*			
	AR	*IFT52*			
	AR	*TRAF3IP1*			
	AR	*CFAP410*			Basal body
	AR	*CEP120*			Centrosome
	AR	*KIAA0586*			
	AR	*KIAA0753*			
SRPS type 2 (Majewski)	AR	*DYNC2H1*	263520	93269	
	AR	*NEK1*			
	AR	*IFT81*			
	AR	*TRAF3IP1*			
SRPS type 4 (Beemer)	AR	*IFT122*	269860	93268	
	AR	*IFT80*			
SRPS type 5	AR	*WDR35*	614091	1505	
SRPS unclassified	AR	*ICK*			
	AR	*INTU*			
	AR	*FUZ*			
	AR	*IFT43*			
	AR	*WDR35*			
Orofaciodigital syndrome type 4 (Mohr–Majewski)	AR	*TCTN3*	258860	2753	
Orofaciodigital syndrome type 2 (Mohr syndrome)	AR	*NEK1*	252100	2751	There are also overlapping OFD phenotypes due to mutations in *INTU*, *CEP120*, and *C2CD3*
Cranioectodermal dysplasia (Levin–Sensenbrenner) type 1, 2	AR	*IFT122*	218330	1515	
	AR	*WDR35*			
	AR	*WDR19*			
	AR	*IFT43*			
	AR	*IFT52*			
Mainzer–Saldino syndrome	AR	*IFT140*	266920	140969	
	AR	*IFT172*			
Axial spondylometaphyseal dysplasia	AR	*CFAP410*	602271	168549	
	AR	*NEK1*			
Thoracolaryngopelvic dysplasia (Barnes)	AD		187760	3317	
See also paternal UPD14 and cerebrocostomandibular syndrome (group 35)					
10. Multiple epiphyseal dysplasia and pseudoachondroplasia group					
Pseudoachondroplasia (PSACH)	AD	*COMP*	177170	750	
Multiple epiphyseal dysplasia (MED)	AD	*COMP*	132400	93308	Not all MED (-like) cases seem to have mutations in these genes
	AD	*COL9A2*	600204	166002	
	AD	*COL9A3*	600969	166002	
	AD	*MATN3*	607078	93311	
	AD	*COL9A1*	614135	166002	
Stickler syndrome, recessive type	AR	*COL9A1*	614134	250984	See also groups 2 and 3
	AR	*COL9A2*	614284		
	AR	*COL9A3*	120270		
See also multiple epiphyseal dysplasia, recessive type in groups 4 and 20 as well as Angel-shaped phalango-epiphyseal dysplasia (ASPED) in group 15					

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
11. Metaphyseal dysplasias					
Metaphyseal dysplasia, Schmid type (MCS)	AD	*COL10A1*	156500	174	
Cartilage-hair hypoplasia (CHH; metaphyseal dysplasia, McKusick type)	AR	*RMRP*	250250	175	Includes anauxetic dysplasia
Metaphyseal dysplasia, POP1 type	AR	*POP1*	617396	93347	Includes anauxetic dysplasia
Metaphyseal dysplasia, Jansen type	AD	*PTHR1*	156400	33067	Activating mutations—see also Blomstrand dysplasia (group 23)
Eiken dysplasia	AR	*PTHR1*	600002	79106	Activating mutations—see also Blomstrand dysplasia (group 23)
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman–Bodian–diamond syndrome, SBDS)	AR AR AR AD	*SBDS* *EFL1* *DNAJC21* *SRP54*	260400 617941	811	
Metaphyseal anadysplasia type 1	AD, AR	*MMP13*	602111	1040	Includes SEMD Missouri type.
Metaphyseal anadysplasia type 2	AR	*MMP9*	613073	1040	
Metaphyseal dysplasia, Spahr type	AR	*MMP13*	250400	2501	
Metaphyseal dysplasia with maxillary hypoplasia	AD	*RUNX2*	156510	2504	May cause multiple vertebral fractures due to osteoporosis
12. Spondylometaphyseal dysplasias (SMD)					
Spondyloenchondrodysplasia (SPENCD)	AR	*ACP5*	271550	1855	Includes combined immunodeficiency with autoimmunity and spondylometaphyseal dysplasia (OMIM 607944)
Odontochondrodysplasia (ODCD)	AR	*TRIP11*	184260	166272	See also achondrogenesis type IA in group 14; may represent a phenotypic spectrum
SMD, Sutcliffe type or corner fractures type	AD	*FN1*	184255	93315	Some cases are linked to *COL2A1* but not the original family
SMD with cone-rod dystrophy	AR	*PCYT1A*	608940	85167	
SMD with corneal dystrophy	AR	*PLCB3*			
See also SMD Kozlowski type (group 8), SMD Sedaghatian type (group 14) and axial SMD (group 9); there are many individual reports of SMD variants.					
13. Spondylo-epi-(meta)-physeal dysplasias (SE(M)D)					
Dyggve–Melchior–Clausen dysplasia (DMC)	AR AR	*DYM* *RAB33B*	223800 615222	239	Includes Smith–McCort dysplasia (OMIM 607326)
Immuno-osseous dysplasia (Schimke)	AR	*SMARCAL1*	242900	1830	
SED with diabetes mellitus, Wolcott–Rallison type	AR	*EIF2AK3*	226980	1667	
SEMD, Matrilin type	AR	*MATN3*	608728	156728	See also matrilin-related MED in group 10
SEMD, Shohat type	AR	*DDRGK1*	602557	93352	
SEMD with leukodystrophy, AIFM1 type	XL	*AIFM1*	300232	168484	
SEMD, biglycan type	XL	*BGN*	300106	93349	Previously known as SEMD, Camera type
SEMD with immune deficiency, EXTL3 type	AR	*EXTL3*	617425	508533	Also known as Immunoskeletal dysplasia with neurodevelopmental abnormalities; see also immuno-osseous dysplasia (Schimke)

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
SEMD with intellectual disability, NANS type	AR	*NANS*	610442	168454	Also known as SEMD, Genevieve type
SEMD with intellectual disability, RSPRY1 type	AR	*RSPRY1*	616723	457395	Also known as SEMD, Faden–Alkuraya type
SEMD, TMEM165 type	AR	*TMEM165*	614727	314667	Congenital disorder of glycosylation type IIk
SEMD, PISD type	AR	*PISD*			Phenotypically variable; see also case reported by Liberfarb RM et al. (PMID: 3561949)
SEMD, UFSP2 type	AD	*UFSP2*	617974 142669	2114	Includes familial hip dysplasia (Beukes)
SEMD, short limb–abnormal calcification type	AR	*DDR2*	271665	93358	See also other dysplasias with stippling in group 21
SED tarda, X-linked (SED-XL)	XL	*TRAPPC2*	313400	93284	
Ehlers–Danlos syndrome, spondylodysplastic type	AR	*SLC39A13*	612350	157965	
SPONASTRIME dysplasia	AR	*TONSL*	271510	93357	
Platyspondyly (brachyolmia) with amelogenesis imperfecta	AR	*LTBP3*	601216	2899	
CODAS syndrome	AR	*LONP1*	600373	1458	
EVEN-PLUS syndrome	AR	*HSPA9*	616854	496751	
CAGSSS syndrome	AR	*IARS2*	616007	436174	
Steel syndrome	AR	*COL27A1*	615155	438117	
See also opsismodysplasia (group 14), mucopolysaccharidosis type 4 (Morquio syndrome), and other conditions in group 27, as well as PPRD (SED with progressive arthropathy) in group 31					
14. Severe spondylodysplastic dysplasias					
Achondrogenesis type 1A (ACG1A)	AR	*TRIP11*	200600	93299	
Schneckenbecken dysplasia	AR	*SLC35D1*	269250	3144	
Spondylometaphyseal dysplasia, Sedaghatian type	AR	*GPX4*	250220	93317	
Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like)	AR	*SBDS*			
Opsismodysplasia	AR	*INPPL1*	258480	2746	Includes lethal and milder cases
MAGMAS related skeletal dysplasia	AR	*PAM16*	613320	401979	
See also thanatophoric dysplasia, types 1 and 2 (group 1); achondrogenesis type 2 and Torrance dysplasia (group 2); fibrochondrogenesis (group 3); achondrogenesis type 1B (group 4); and metatropic dysplasia (group 8)					
15. Acromelic dysplasias					
Trichorhinophalangeal dysplasia types 1/3	AD	*TRPS1*	190350 190351	77258	
Trichorhinophalangeal dysplasia type 2 (Langer–Giedion)	AD	*TRPS1 and EXT1*	150230	502	Microdeletion syndrome; see also multiple cartilaginous exostoses in group 29
Acrocapitofemoral dysplasia	AR	*IHH*	607778	63446	

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Geleophysic dysplasia	AR AD AD	*ADAMTSL2* *FBN1* *LTBP3*	231050 614185 617809	2623	Some forms unlinked to either gene
Acromicric dysplasia	AD AD	*FBN1* *LTBP3*	102370	969	Includes acrolaryngeal dysplasia, previously known as Fantasy Island dysplasia or Tattoo dysplasia, and Moore–Federman syndrome
Weill–Marchesani syndrome	AD AR AR AR	*FBN1* *ADAMTS10* *ADAMTS17* *LTBP2*	608328 277600 613195 614819	3449	
Myhre dysplasia	AD	*SMAD4*	139210	2588	
Acrodysostosis	AD AD	*PDE4D* *PRKAR1A*	614613 101800	950	Includes acroscyphodysplasia (PMID 30006632)
ASPED	AD		105835	63442	Possibly related or allelic to brachydactyly type C
Leri Pleonosteosis	AD	8q22.1	151200	2900	Duplication at 8q22.1 encompassing *GDF6* and *SDC2*
SED, MIR140 type	AD	MIR140			Brachydactyly with cone-shaped epiphyses
See also brachydactyly group (groups 37 and 38)					
16. Acromesomelic dysplasias					
Acromesomelic dysplasia type Maroteaux (AMDM)	AR	*NPR2*	602875	40	
Grebe dysplasia	AR AR	*GDF5* *BMPR1B*	200700 609441	2098	Includes acromesomelic dysplasia Hunter–Thompson type and acromesomelic dysplasia with genital anomalies; see also brachydactylies (group 37)
Fibular hypoplasia and complex brachydactyly (Du pan)	AR AR	*GDF5* *BMPR1B*	228900	2639	See also brachydactylies (group 37)
Acromesomelic dysplasia, Osebold–Remondini type	AD		112910	93437	
17. Mesomelic and rhizo-mesomelic dysplasias					
Dyschondrosteosis (Leri–Weill)	Pseudo-AD	*SHOX*	127300	240	Includes Reinhardt–Pfeiffer dysplasia (OMIM 191400)
Mesomelic dysplasia, Langer type	Pseudo-AR	*SHOX*	249700	2632	
Omodysplasia, recessive type	AR	*GPC6*	258315	93329	
Omodysplasia, dominant type	AD	*FZD2*	164745	93328	See also Robinow syndrome, dominant type
Robinow syndrome, recessive type	AR AR	*ROR2* *NXN*	268310	1507	Includes previous COVESDEM (costo-vertebral segmentation defect with mesomelia); see also brachydactyly type B
Robinow syndrome, dominant type	AD AD AD AD	*WNT5A* *DVL1* *DVL3* *FZD2*	180700 616331 616894	3107	
Mesomelic dysplasia, Kantaputra type	AD	*HOXD*	156232	1836	Duplications at HOXD gene cluster locus; includes mesomelic dysplasia, Korean type

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
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	*SULF1 and SLCO5A1*	600383	2496	Microdeletion syndrome involving two adjacent genes
Mesomelic dysplasia, Savarirayan type (triangular tibia-fibular aplasia)	AD	*ID4*	605274	85170	Microdeletions on 6p22.3; Microdeletion on 2q11.2 encompassing *LAF4* can cause a phenotype with overlapping skeletal features (PMID 18616733)
See also Werner syndrome (group 39); also consider: mesomelic dysplasia, Camera type (OMIM 611886) and mesomelic dysplasia, Fryns type (PMID 3342548)					
18. Bent bone dysplasia group					
Campomelic dysplasia (CD)	AD	*SOX9*	114290	140	Includes acampomelic campomelic dysplasia (ACD), mild campomelic dysplasia (OMIM 602196) and isolated Pierre–Robin sequence
Stüve–Wiedemann dysplasia	AR	*LIFR*	601559	3206	Includes former neonatal Schwartz–Jampel syndrome or SJS type 2
Kyphomelic dysplasia, several forms			211350	1801	Probably heterogeneous
Bent bone dysplasia	AD	*FGFR2*	614592	313855	
Bent bones can also been observed in conditions with osseous fragility (group 25)					
19. Primordial dwarfism and slender bones group					
3-M syndrome	AR AR AR	*CUL7* *OBSL1* *CCDC8*	273750 612921 614205	2616	Includes dolichospondylic dysplasia and Yakut short stature syndrome
Sanjad–Sakati syndrome	AR	*TBCE*	241410	93324	Referred to in OMIM as Kenny–Caffey type 1 but does not correspond to the disorder described by Kenny and Caffey which is the dominant form
Kenny–Caffey syndrome	AD	*FAM111A*	127000	93325	
Osteocraniostenosis	AD	*FAM111A*	602361	2763	
Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1)	AR	*RNU4ATAC*	210710	2636	Usually homozygous mutations; Includes Taybi–Linder cephaloskeletal dysplasia
Roifman syndrome	AR	*RNU4ATAC*	616651	353298	
Multiple epiphyseal dysplasia with microcephaly and nystagmus (Lowry–Wood syndrome)	AR	*RNU4ATAC*	226960	1824	See also group 10 because of multiple epiphyseal dysplasia
Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type)	AR	*PCNT2*	210720	2637	
Microcephalic osteodysplastic primordial dwarfism (other types)	AR AR AR AR AR AR AR AR AR	*ATR* *RBBP8* *CEP152* *DNA2* *TRAIP* *NSMCE2* *CENPE* *CRIPT* *XRCC4*	210600 606744 613823 615807 616777 617253 616051 615789 616541		Seckel syndrome 1 Seckel syndrome 2 Seckel syndrome 5 Seckel syndrome 8 Seckel syndrome 9 Seckel syndrome 10 Overlaps with primary microcephaly syndromes

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
IMAGE syndrome (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies)	AD AR	*CDKN1C* *POLE*	614732 618336	85173	 With immunodeficiency
Hallermann–Streiff syndrome	AR		234100	2108	
Saul–Wilson syndrome	AD	*COG4*	618150	85172	
20. Dysplasias with multiple joint dislocations					
Desbuquois dysplasia type 1 (with accessory ossification center in index finger)	AR	*CANT1*	251450	1425	There are also cases with or without accessory ossification centers unlinked to CANT1
Desbuquois dysplasia with short metacarpals and elongated phalanges (Kim type)	AR	*CANT1*	251450	1425	
Desbuquois dysplasia type 2 (Baratela–Scott syndrome)	AR	*XYLT1*	615777	1425	
Multiple epiphyseal dysplasia, recessive type	AR	*CANT1*	617719		Classified in OMIM as EDM7; very rare form of MED
SEMD with joint laxity (SEMD-JL), leptodactylic or Hall type	AD	*KIF22*	603546	93360	
SEMD with joint laxity (SEMD-JL), Beighton type	AR	*B3GALT6*	271640	93359	
SEMD with joint laxity (SEMD-JL), EXOC6B type	AR	*EXOC6B*	618395	93359	Phenotype resembles SEMD-JL leptodactylic or Hall type
Pseudodiastrophic dysplasia	AR		264180	85174	
CSGALNACT1 deficiency (joint dislocations and mild skeletal dysplasia	AR	*CSGALNACT1*	616615		
B3GAT3 deficiency	AR	*B3GAT3*	245600	284139	Multisystem linkeropathy including osteopenia with fractures (osteogenesis imperfecta-like) and dislocations (Larsen-like) and developmental delay
Short stature with joint laxity and myopia	AR	*GZF1*	617662	527450	Phenotype resembles Larsen syndrome
Multiple joint dislocations with amelogenesis imperfecta	AR	*SLC10A7*	618363		
Severe (lethal) neonatal short limb dysplasia with multiple dislocations	AR	*FAM20B*			Phenotype resembles Desbuquois dysplasia
Ehlers–Danlos syndrome, kyphoscoliotic type 1	AR	*PLOD1*	225400	1900	
Ehlers–Danlos syndrome, kyphoscoliotic type 2	AR	*FKBP14*	614557	300179	
See also SED with congenital dislocations, CHST3 type (group 4); atelosteogenesis type 3 and Larsen syndrome (group 7); B4GALT7 deficiency in group 25					
21. Chondrodysplasia punctata (CDP) group					
CDP, X-linked dominant, Conradi–Hünermann type (CDPX2)	XL	*EBP*	302960	35173	
CDP, X-linked recessive, brachytelephalangic type (CDPX1)	XL	*ARSE*	302950	79345	
CHILD (congenital hemidysplasia, ichthyosis, limb defects)	XL	*NSDHL*	308050	139	
Keutel syndrome	AR	*MGP*	245150	85202	
Greenberg dysplasia	AR	*LBR*	215140	1426	Includes hydrops-ectopic calcification-moth-eaten appearance dysplasia (HEM) and dappled diaphyseal dysplasia

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Rhizomelic CDP	AR AR AR AR AR	*PEX7* *DHPAT* *AGPS* *FAR1* *PEX5*	215100 222765 600121 616154 616716	177	
CDP tibial-metacarpal type	AD, AR		118651	79346	
Astley–Kendall dysplasia	AR?			85175	Relationship to OI and to Greenberg dysplasia unclear
Note that stippling can occur in maternal autoimmune disease and several syndromes such as Zellweger, Smith-Lemli–Opitz and others. See also SEMD short limb-abnormal calcification type in group 13.					
22. Neonatal osteosclerotic dysplasias					
Blomstrand dysplasia	AR	*PTHR1*	215045	50945	Caused by recessive inactivating mutations; see also Eiken dysplasia and Jansen dysplasia
Desmosterolosis	AR	*DHCR24*	602398	35107	See also other sterol-metabolism related conditions
Caffey disease (including prenatal, infantile and attenuated forms)	AD	*COL1A1*	114000	1310	See also osteogenesis imperfecta related to collagen 1 genes (group 25)
Caffey dysplasia (severe variants with prenatal onset)	AR		114000	1310	
Raine dysplasia (lethal and nonlethal forms)	AR	*FAM20C*	259775	1832	Includes lethal and nonlethal cases (milder cases with hypophosphatemic rickets)
Dysplastic cortical hyperostosis, Kozlowski–Tsuruta type	AR?			2204	Two cases reported (see PMID 12401992)
Dysplastic cortical hyperostosis, Al-Gazali type	AR?		601356		
See also Astley–Kendall dysplasia and CDPs in group 21					
23. Osteopetrosis and related disorders					
Osteopetrosis, severe neonatal or infantile forms	AR AR AR	*TCIRG1* *CLCN7* *SNX10*	259700 611490 615085	667	
Osteopetrosis, infantile form, with nervous system involvement (OPTB5)	AR	*OSTM1*	259720	85179	Includes former osteopetrosis with infantile neuraxonal dysplasia (OMIM 600329)
Osteopetrosis, infantile form, osteoclast-poor with immunoglobulin deficiency (OPTB7)	AR	*TNFRSF11A*	612301	178389	*See also* familial expansile osteolysis in the osteolysis group (group 28)
Osteopetrosis, intermediate form	AR AR AR	*TNFSF11* *PLEKHM1* *CLCN7*	259710 611497 259710	667 210110	
Osteopetrosis with renal tubular acidosis (OPTB3)	AR	*CA2*	259730	2785	
Osteopetrosis, late-onset form type 2 (OPTA2)	AD	*CLCN7*	166600	53	
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	XL	*IKBKG*	300301	69088	

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Osteopetrosis, moderate form with defective leucocyte adhesion (LAD3)	AR	*FERMT3*	612840	99844	Also mutations in *RASGRP2* have been reported (PMID 18709451)
Osteosclerotic metaphyseal dysplasia	AR	*LRRK1*	615198	500548	Heterogeneous condition
Pycnodysostosis	AR	*CTSK*	265800	763	
Dysosteosclerosis	AR AR AR	*SLC29A3* *TNFRSF11A* *CSF1R*	224300 224300	1782	Bi-allelic mutations in *CSF1R* cause a dysosteosclerosis-like phenotype
This group is characterized by an impaired bone resorption as common mechanism (osteoclast related) and therefore OPTA1 is not included in this group (see group 24); Note: Osteomesopyknosis may represent a form of osteopetrosis					
24. Other sclerosing bone disorders					
Osteopoikilosis	AD	*LEMD3*	166700	166119 1306	Includes Buschke–Ollendorff syndrome
Melorheostosis with osteopoikilosis	AD	*LEMD3*	166700	1879	Includes mixed sclerosing bone dysplasia
Melorheostosis	SP	*MAP2K1*	155950	2485	Probably locus heterogeneity
Osteopathia striata with cranial sclerosis (OSCS)	XL	*AMER1*	300373	2780	
Craniometaphyseal dysplasia	AD AR	*ANKH* *GJA1*	123000 218400	1522	
Diaphyseal dysplasia Camurati–Engelmann	AD	*TGFB1*	131300	1328	Probably locus heterogeneity
Hyperostosis–Hyperphosphatemia syndrome	AR AR AR	*GALNT3* *FGF23* *KL*	211900 617993 617994	306661	
Cerebellar hypoplasia-endosteal sclerosis	AR	*POLR3B*	213002	85186	
Hematodiaphyseal dysplasia Ghosal	AR	*TBXAS1*	231095	1802	
Hypertrophic osteoarthropathy	AR AR	*HPGD* *SLCO2A1*	259100 614441	248095	Includes cranio-osteoarthropathy and cases of recessive pachydermoperiostosis
Pachydermoperiostosis (hypertrophic osteoarthropathy, primary, autosomal dominant)	AD		167100	2796	Relationship to recessive form (OMIM 259100, HPGD deficiency) unclear
Oculodentoosseous dysplasia (ODOD) mild type	AD	*GJA1*	164200	2710	
Oculodentoosseous dysplasia (ODOD) severe type	AR	*GJA1*	257850	2710	Possibly homozygous form of mild ODOD
Osteoectasia with hyperphosphatasia (juvenile Paget disease)	AR	*TNFRSF11B*	239000	2801	
Osteosclerosis	AD	*LRP5*	144750	2790 2783 3416	Includes AD osteopetrosis type 1 (OPTA1) (OMIM 607634) and endosteal hyperostosis, Worth type; see note for group 23
Sclerosteosis	AR AR	*SOST* *LRP4*	269500 614305	3152	
Endosteal hyperostosis, van Buchem type	AR	*SOST*	239100	3416	Specific 52 kb deletion downstream of *SOST*
Trichodentoosseous dysplasia	AD	*DLX3*	190320	3352	
Diaphyseal medullary stenosis with malignant fibrous histiocytoma	AD	*MTAP*	112250	85182	Also known as Hardcastle syndrome
Craniodiaphyseal dysplasia	AD	*SOST*	122860	1513	Dominant negative

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Craniometadiaphyseal dysplasia, Wormian bone type	AR		269300	85184	
Lenz–Majewski hyperostotic dysplasia	AD	*PTDSS1*	151050	2658	
Metaphyseal dysplasia, Braun–Tinschert type	AD		605946	85188	
Pyle disease	AR	*SFRP4*	265900	3005	
In this group, many disorders have an increased bone formation as common mechanism (osteoblast related). Consider also mesomelic dysplasia Robinow type (*DVL1*) (group 17) and trichothiodystrophy with central osteosclerosis (PMID 15148554)					
25. Osteogenesis Imperfecta and decreased bone density group					
Osteogenesis imperfecta, nondeforming with persistently blue sclerae (OI type 1)	AD	*COL1A1* *COL1A2*	166200	216796	OMIM OI type I
Osteogenesis imperfecta, perinatal lethal form (OI type 2)	AD	*COL1A1*	166210	216804	OMIM OI type II
	AD	*COL1A2*	166210	216804	OMIM OI type II
	AR	*CRTAP*	610854	216804	OMIM OI type VII
	AR	*LEPRE1*	610915	216804	OMIM OI type VIII
	AR	*PPIB*	259440	216804	OMIM OI type IX
Osteogenesis imperfecta, progressively deforming type (OI type 3)	AD	*COL1A1*	259420	216812	OMIM OI type III
	AD	*COL1A2*	259420	216812	OMIM OI type III
	AD	*IFITM5*	610967	216812	OMIM OI type V
	AR	*SERPINF1*	613982	216812	OMIM OI type VI
	AR	*CRTAP*	610682	216812	OMIM OI type VII
	AR	*LEPRE1*	610915	216812	OMIM OI type VIII
	AR	*PPIB*	259440	216812	OMIM OI type IX
	AR	*SERPINH1*	613848	216812	OMIM OI type X
	AR	*FKBP10*	610968	216812	OMIM OI type XI
	AR	*TMEM38B*	615066	216812	OMIM OI type XIII
	AR	*BMP1*	112264	216812	OMIM OI type XIV
	AR	*WNT1*	615220	216812	OMIM OI type XV
	AR	*CREB3L1*	616229	216812	OMIM OI type XVI
	AR	*SPARC*	616507	216812	OMIM OI type XVII
	AR	*TENT5A*	617952	216812	OMIM OI type XVIII
Osteogenesis imperfecta, moderate form (OI type 4) (Note: In adults always, normal sclerae)	AD	*COL1A1*	166220	216820	OMIM OI type IV
	AD	*COL1A2*	166220	216820	OMIM OI type IV
	AD	*WNT1*	615220	216820	OMIM OI type XV
	AD	*IFITM5*	610967	216820	OMIM OI type V
	AR	*CRTAP*	610682	216820	OMIM OI type VII
	AR	*PPIB*	259440	216820	OMIM OI type IX
	AR	*FKBP10*	610968	216820	OMIM OI type XI
	AR	*SP7*	613849	216820	OMIM OI type XII
Osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus (OI type 5)	AD	*IFITM5*	610967	216828	
Osteoporosis—X-linked form	XL	*PLS3*	300910	391330	OMIM OI type XIX
	XL	*MBTPS2*	301014		
Osteoporosis—AD form	AD	*WNT1*	615220	216820	OMIM OI type XV
	AD	*LRP5*	166710	85193	
Bruck syndrome type 1 (BS1)	AR	*FKBP10*	259450	2771	See autosomal recessive OI, above; intrafamilial variability between OI type 3, arthrogryposis and BS1 documented
Bruck syndrome type 2 (BS2)	AR	*PLOD2*	609220	2771	

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Osteoporosis-pseudoglioma syndrome	AR	*LRP5*	259770	2788	May mimic OI types 3 and 4 without eye involvement
Calvarial doughnut lesions with bone fragility	AD	*SGMS2*	126550	85192	Overlap with SMD phenotype
Cole–Carpenter dysplasia (bone fragility with craniosynostosis)	AD	*P4HB*	112240	2050	
Cole–Carpenter like dysplasia	AR	*SEC24D*	616294		Cole–Carpenter syndrome 2
Spondylo-ocular dysplasia	AR	*XYLT2*	605822	85194	
Gnathodiaphyseal dysplasia	AD	*ANO5*	166260	53697	
Ehlers–Danlos syndrome, spondylodysplastic type	AR	*B4GALT7*	130070	75497	Formerly known as "EDS, progeroid form"; also known as "Larsen syndrome, la Réunion variant"; see also B3GALT6 deficiency in group 20
Geroderma osteodysplasticum	AR	*GORAB*	231070	2078	
Cutis laxa, autosomal recessive form, type 2B (ARCL2B)	AR	*PYCR1*	612940	90350	Skeletal features overlapping with progeroid EDS and geroderma osteodysplasticum
Cutis laxa, autosomal recessive form, type 2A (ARCL2A) (Wrinkly skin syndrome)	AR	*ATP6VOA2*	278250 219200	90350	Skeletal features overlapping with progeroid EDS and geroderma osteodysplasticum
Wiedemann–Rautenstrauch syndrome	AR	*POLR3A*	264090	3455	
Singleton–Merten dysplasia type 1	AD	IFIH1	182250	85191	
Singleton–Merten dysplasia type 2	AR	DDX58	616298	85191	
Short stature, optic nerve atrophy and Pelger–Huet anomaly (SOPH syndrome)	AR	NBAS	614800	391677	
See also metaphyseal dysplasia with maxillary hypoplasia in group 11					
26. Abnormal mineralization group					
Hypophosphatasia, perinatal lethal, infantile and juvenile forms	AR	*ALPL*	241500	436	
Hypophosphatasia, juvenile and adult forms	AD	*ALPL*	146300	247676	Includes odontohypophosphatasia
Hypophosphatemic rickets, X-linked	XL	*PHEX*	307800	89936	
Hypophosphatemic rickets, autosomal dominant	AD	*FGF23*	193100	89937	
Hypophosphatemic rickets, autosomal recessive, type 1 (ARHR1)	AR	*DMP1*	241520	289176	
Hypophosphatemic rickets, autosomal recessive, type 2 (ARHR2)	AR	*ENPP1*	613312	289176	
Hypophosphatemic rickets with hypercalciuria, X-linked	XL	*CLCN5*	300554	1652	Part of Dent's disease complex
Hypophosphatemic rickets with hypercalciuria, autosomal recessive (HHRH)	AR	*SLC34A3*	241530	157215	
Vitamin D-dependent rickets, type 1A	AR	*CYP27B1*	264700	289157	
Vitamin D-dependent rickets, type 1B	AR	*CYP2R1*	600081	289157	
Vitamin D-dependent rickets, type 2A	AR	*VDR*	277440	93160	
Vitamin D-dependent rickets, type 2B	AR?		600785	93160	
Familial hyperparathyroidism, types 1–4	AD AD AD AD	*CDC73* *CDC73* - *GCM2*	145000 145001 610071 617343	99879 99880 99879 99879	Genetic hyperparathyroidism due to parathyroid adenoma occurs in a number of tumor-associated syndromes such as MEN
Neonatal hyperparathyroidism, severe form	AR, AD	*CASR*	239200	417	

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Neonatal hyperparathyroidism, transient form	AR	*TRPV6*	618188	417	
Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism	AD	*CASR*	145980	405	Other forms of familial hypocalciuric hypercalcemia do not show significant skeletal phenotypes
Calcium pyrophosphate deposition disease (familial chondrocalcinosis) type 2	AD	*ANKH*	118600	1416	Loss-of-function mutations (see craniometaphyseal dysplasia in group 24)
Cutaneous skeletal hypophosphatemia syndrome	SP SP	*HRAS* *NRAS*			
See also Jansen dysplasia and Eiken dysplasia (group 11) and Cole–Carpenter syndrome (group 25); see also group 22 for *FAM20C* related cases of hypophosphatemic rickets					
27. Lysosomal storage diseases with skeletal involvement (dysostosis multiplex group)					
Mucopolysaccharidosis type 1H-1S	AR	*IDUA*	607014 607015 607016	579	
Mucopolysaccharidosis type 2	XL	*IDS*	309900	580	
Mucopolysaccharidosis type 3A	AR	*SGSH*	252900	79269	
Mucopolysaccharidosis type 3B	AR	*NAGLU*	252920	79270	
Mucopolysaccharidosis type 3C	AR	*HSGNAT*	252930	79271	
Mucopolysaccharidosis type 3D	AR	*GNS*	252940	79272	
Mucopolysaccharidosis type 4A	AR	*GALNS*	253000	309297	
Mucopolysaccharidosis type 4B	AR	*GLB1*	253010	309310	
Mucopolysaccharidosis type 6	AR	*ARSB*	253200	583	
Mucopolysaccharidosis type 7	AR	*GUSB*	253220	584	
Mucopolysaccharidosis-plus syndrome (VPS33A deficiency)	AR	*VPS33A*	617303	505248	
Fucosidosis	AR	*FUCA*	230000	349	
Alpha-Mannosidosis	AR	*MAN2B1*	248500	61	
Beta-Mannosidosis	AR	*MANBA*	248510	118	
Aspartylglucosaminuria	AR	*AGA*	208400	93	
GM1 Gangliosidosis, several forms	AR	*GLB1*	230500	354	
Sialidosis, several forms	AR	*NEU1*	256550	812 93399 93400	
Sialic acid storage disease (SIASD)	AR	*SLC17A5*	269920	834	
Galactosialidosis, several forms	AR	*PPGB*	256540	351	
Multiple sulfatase deficiency	AR	*SUMF1*	272200	585	
Mucolipidosis II (I-cell disease), alpha/beta type	AR	*GNPTAB*	252500	576	
Mucolipidosis III (pseudo-Hurler polydystrophy), alpha/beta type	AR	*GNPTAB*	252600	423461	
Mucolipidosis III (pseudo-Hurler polydystrophy), gamma type	AR	*GNPTG*	252605	423470	
Other conditions resembling storage diseases: congenital disorders of glycosylation and geleophysic dysplasia (group 15)					

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
28. Osteolysis group					
Familial expansile osteolysis	AD	*TNFRSF11A*	174810 602080	85195	Includes early-onset familial Paget disease of bone. See also osteopetrosis and dysosteosclerosis (group 23)
Mandibuloacral dysplasia	AR AR	*LMNA* *ZMPSTE24*	248370 608612	2457	
Progeria, Hutchinson–Gilford type	AD	*LMNA*	176670	740	
Multicentric osteolysis, nodulosis and arthropathy (MONA)	AR AR	*MMP2* *MMP14*	259600 277950	371428	Includes Winchester–Torg syndrome and nodulosis-arthropathy-osteolysis syndrome
Hajdu–Cheney syndrome	AD	*NOTCH2*	102500	955	Includes serpentine fibula-polycystic kidney syndrome
Multicentric carpal-tarsal osteolysis with and without nephropathy	AD	*MAFB*	166300	2774	
See also pycnodysostosis, cleidocranial dysplasia, Keutel syndrome, Farber disease and Singleton-Merten syndrome. Note: several neurologic conditions may cause acro-osteolysis					
29. Disorganized development of skeletal components group					
Multiple cartilaginous exostoses (osteochondromas)	AD AD	*EXT1* *EXT2*	133700 133700	321 321	
Cherubism	AD	*SH3BP2*	118400	184	
Fibrous dysplasia, polyostotic form (McCune–Albright)	SP	*GNAS*	174800	562	Somatic mosaicism and imprinting phenomena
Metachondromatosis	AD	*PTPN11*	156250	2499	
Osteoglophonic dysplasia	AD	*FGFR1*	166250	2645	Craniosynostosis is also an important feature (group 33)
Fibrodysplasia ossificans progressiva (FOP)	AD	*ACVR1*	135100	337	
Neurofibromatosis type 1 (NF1)	AD	*NF1*	162200	363700	
Cherubism with gingival fibromatosis (Ramon syndrome)	AR		266270	3019	
Dysplasia epiphysealis hemimelica (Trevor)	SP		127800	1822	
Lipomembraneous osteodystrophy with leukoencephalopathy (presenile dementia with bone cysts; Nasu–Hakola)	AR	*TREM2*, *TYROBP*	221770	2770	
Enchondromatosis (Ollier) and Enchondromatosis with hemangiomata (Maffucci)	SP	*IDH1*, *IDH2*	166000	296 163634	
Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria	SP	*IDH1*	614875	99646	
Genochondromatosis	AD		137360	85197 93398	Probably includes Vaandrager–Peña syndrome
Gorham-stout disease	SP		123880	73	See also familial diffuse cystic angiomatosis of bone (PMID 2910603)
Osteofibrous dysplasia	AD, SP	*MET*	607278	488265	
See also Proteus syndrome in group 30; spondyloenchondrodysplasia in group 12; dysspondyloenchondromatosis in group 2; cutaneous skeletal hypophosphatemia syndrome in group 26					

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
30. Overgrowth (tall stature) syndromes with skeletal involvement					
Weaver syndrome	AD	*EZH2*	277590	3447	Some cases reported with *NSD1*, *EED*, and *SUZ12* mutations
Sotos syndrome	AD AD AR	*NSD1* *NFIX* *APC2*	117550 614753 617169	821 420179	Includes Malan syndrome
Luscan–Lumish syndrome	AD	*SETD2*	616831		
Tatton–Brown–Rahman syndrome	AD	*DNMT3A*	615879	404443	
Marshall–Smith syndrome	AD	*NFIX*	602535	561	
Proteus syndrome	SP	*AKT1*	176920	744	
CLOVES	SP	*PIK3CA*	612918	140944	
Marfan syndrome	AD	*FBN1*	154700	558	
Congenital contractural arachnodactyly	AD	*FBN2*	121050	115	
Loeys–Dietz syndrome (types 1–6)	AD AD AD AD AD AD	*TGFBR1* *TGFBR2* *SMAD3* *TGFB2* *TGFB3* *SMAD2*	609192 610168 613795 614816 615582 601366	60030	
Meester–Loeys syndrome	XL	*BGN*	300989		See also SEMD, biglycan type (group 13)
Overgrowth syndrome with 2q37 translocations	SP	*NPPC*		498488	Overgrowth probably caused by overexpression of *NPPC*
Tall stature with long halluces, NPR2 type	AD	*NPR2*	615923	329191	Includes epiphyseal chondrodysplasia, Miura type; gain-of-function mutations
Tall stature with long halluces, NPR3 type	AR	*NPR3*			Loss-of-function mutations
Moreno–Nishimura–Schmidt syndrome	SP		608811	498485	
See also Shprintzen–Goldberg syndrome in Craniosynostosis group 33					
31. Genetic inflammatory/rheumatoid-like osteoarthropathies					
Progressive pseudorheumatoid dysplasia (PPRD; SED with progressive arthropathy)	AR	*WISP3*	208230	1159	
Chronic infantile neurologic cutaneous articular syndrome (CINCA) / neonatal onset multisystem inflammatory disease (NOMID)	AD	*CIAS1*	607115	1451	
Sterile multifocal osteomyelitis, periostitis, and pustulosis (CINCA/NOMID-like)	AR	*IL1RN*	147679	210115	
Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anemia (CRMO with CDA; Majeed syndrome)	AR	*LPIN2*	609628	77297	
Hyaline Fibromatosis syndrome	AR	*ANTXR2*	236490	2176	Previously known as infantile systemic hyalinosis, juvenile hyaline fibromatosis (OMIM 228600) and puretic syndrome
32. Cleidocranial dysplasia and related disorders					
Cleidocranial dysplasia	AD	*RUNX2*	119600	1452	See also metaphyseal dysplasia with maxillary hypoplasia (group 11)

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
CDAGS syndrome (craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, genital anomalies, skin eruption)	AR		603116	85199	
Yunis–Varon dysplasia	AR AR	*FIG4* *VAC14*	216340	3472	
Parietal foramina (isolated)	AD AD	*ALX4* *MSX2*	609597 168500	60015	See also frontonasal dysplasia type 1 (group 34)
Parietal foramina with cleidocranial dysplasia	AD	*MSX2*	168550	251290	*MSX2* mutations also cause craniosynostosis Boston type (group 33)
See also pycnodysostosis (group 23), wrinkly skin syndrome, mandibuloacral dysplasia, progeria and Hajdu–Cheney syndrome (group 28) for similar clavicular defects.					
33. Craniosynostosis syndromes					
Pfeiffer syndrome	AD AD	*FGFR1* *FGFR2*	101600 101600	93258 710	Most have *FGFR1* p.P252R mutation; Includes Jackson–Weiss syndrome (OMIM 123150)
Apert syndrome	AD	*FGFR2*	101200	87	
Craniosynostosis with cutis gyrata (Beare–Stevenson)	AD	*FGFR2*	123790	1555	
Crouzon syndrome	AD	*FGFR2*	123500	207	
Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome)	AD	*FGFR3*	612247	93262	Defined by specific *FGFR3* p. A391E mutation
Craniosynostosis, Muenke type	AD	*FGFR3*	602849	53271	Defined by specific *FGFR3* p. P250R mutation
Antley–Bixler syndrome	AR	*POR*	201750	83 63269	
Craniosynostosis Boston type	AD	*MSX2*	604757	1541	Heterozygous p.P148H mutation in two families
Saethre–Chotzen syndrome	AD	*TWIST1*	101400	794	Mutations in *FGFR3*, *FGFR2*, and *TCF12* have been reported to cause phenotypes resembling Saethre–Chotzen syndrome
Shprintzen–Goldberg syndrome	AD	*SKI*	182212	2462	
Baller–Gerold syndrome	AR	*RECQL4*	218600	1225	
Carpenter syndrome	AR AR	*RAB23* *MEGF8*	201000 614976	65759	
Coronal craniosynostosis	AD	*TCF12*	615314	35099	
Complex craniosynostosis	AD	*ERF*	600775		Mutations in *ERF* also cause Chitayat hyperphalangism syndrome
See also cranioectodermal dysplasia (group 9), SEMD type RSPRY1 (group 13), osteocraniostenosis (group 19), Cole–Carpenter syndrome (group 25), CDAGS syndrome (group 32), craniofrontonasal syndrome (group 34), Philadelphia type craniosynostosis (IHH duplication) (group 41) and multiple synostosis syndrome FGF9 type (group 42). Craniosynostosis can also be present in Loeys–Dietz syndrome (group 30)					

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
34. Dysostoses with predominant craniofacial involvement					
Mandibulofacial dysostosis (Treacher Collins, Franceschetti–Klein)	AD AR AD, AR	*TCOF1* *POLR1C* *POLR1D*	154500 248390 613717	861	
Mandibulofacial dysostosis with microcephaly	AD	*EFTUD2*	610536	79113	
Mandibulofacial dysostosis with alopecia	AD	*EDNRA*	616367	443995	
Miller syndrome (postaxial acrofacial dysostosis)	AR	*DHODH*	263750	246	
Acrofacial dysostosis, Nager type	AD, AR	*SF3B4*	154400	245	
Acrofacial dysostosis, Rodriguez type	AR	*SF3B4*	201170	1788	
Acrofacial dysostosis, Cincinnati type	AD	*POLR1A*	616462	1200	
Frontonasal dysplasia, type 1	AR	*ALX3*	136760	391474	
Frontonasal dysplasia, type 2	AR	*ALX4*	613451	228390	
Frontonasal dysplasia, type 3	AR	*ALX1*	613456	306542	
Craniofrontonasal syndrome	XL	*EFNB1*	304110	1520	
Acromelic frontonasal dysostosis	AD	*ZSWIM6*	603671	1827	
Hemifacial microsomia	SP, AD		164210	374	Includes Goldenhar syndrome and oculo-auriculo-vertebral spectrum; genetically heterogeneous; in some cases, a microduplication on 14q23.1
Richieri–Costa–Pereira syndrome	AR	*EIF4A3*	268305	3102	
Auriculocondylar syndrome, type 1	AD	*GNAI3*	602483	137888	
Auriculocondylar syndrome, type 2	AR, AD	*PLCB4*	614669	137888	
Auriculocondylar syndrome, type 3	AR	*EDN1*	615706	137888	
Orofaciodigital syndrome type I (OFD1)	XL	*OFD1*	311200	2750	
Weyers acrofacial (acrodental) dysostosis	AD AD	*EVC1* *EVC2*	193530	952	See also Ciliopathies (group 9)
See also orofaciodigital syndrome type IV in the Ciliopathies (group 9)					
35. Dysostoses with predominant vertebral with and without costal involvement					
Currarino syndrome	AD	*MNX1*	176450	1552	Overlap with caudal regression syndrome (see OMIM 600145; heterozygous mutations in *VANGL1*)
Spondylocostal dysostosis	AR AR AR AR AR, AD AR	*DLL3* *MESP2* *LFNG* *HES7* *TBX6* *RIPPLY2*	277300 608681 609813 613686 122600 616566	2311 2311 2311 2311 122600 2311	
NAD deficiency syndrome	AR AR	*HAAO* *KYNU*	617660 617661	521438	With associated cardiac, limb, and renal defects
Vertebral segmentation defect (congenital scoliosis) with variable penetrance	AD AD	*MESP2* *HES7*	608681 613686	2311 2311	
Klippel–Feil syndrome	AD AR AD AR	*GDF6* *MEOX1* *GDF3* *MYO18B*	118100 214300 613702 616549	2345 2345 2345 447974	Role of *GDF6* mutations in AD spondylothoracic dysostosis remains unclear

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Cerebrocostomandibular syndrome (rib gap syndrome)	AD	*SNRPB*	117650	1393	Mutations in *COG1* are found in a cerebrocostomandibular-like syndrome (CDG type IIg)
Diaphanospondylodysostosis	AR	*BMPER*	608022	66637	Includes ischiospinal dysostosis
Spondylo-megaepiphyseal-metaphyseal dysplasia (SMMD)	AR	*NKX3-2*	613330	228387	
See also spondylocarpotarsal synostosis syndrome in group 7					
36. Patellar dysostoses					
Ischiopatellar dysplasia (small patella syndrome)	AD	*TBX4*	147891	1509	
Nail-patella syndrome	AD	*LMX1B*	161200	2614	
Genitopatellar syndrome	AD	*KAT6B*	606170	85201	
Ear-patella-short stature syndrome (Meier–Gorlin)	AR AR AR AR AR AR AD AR	*ORC1* *ORC4* *ORC6* *CDT1* *CDC6* *GMNN* *CDC45L*	224690 613800 613803 613804 613805 616835 617063	2554 2554 2554 2554 2554 2554 2554	
See also MED group (group 10) for conditions with patellar changes as well as ischio-pubic-patellar dysplasia as mild expression of campomelic dysplasia (group 18) and RAPADILINO syndrome (group 39); patellar hypoplasia is variable present in PITX1 related clubfoot (group 39)					
37. Brachydactylies (without extraskeletal manifestations)					
Brachydactyly type A1	AD	*IHH*	112500	93388	
Brachydactyly type A2	AD AD AD	*BMPR1B* *BMP2* *GDF5*	112600 112600 112600	93396	Duplication of *BMP2* enhancer
Brachydactyly type B	AD	*ROR2*	113000	93383	See also Robinow syndrome/ COVESDEM
Brachydactyly type B2	AD	*NOG*	611377	140908	
Brachydactyly type C	AD, AR	*GDF5*	113100	93384	See also ASPED (group 15) and other *GDF5* disorders
Brachydactyly type D	AD	*HOXD13*	113200		Brachydactyly type D is often a component of brachydactyly type E
Brachydactyly type E	AD AD	*PTHLH* *HOXD13*	613382 113300	93387	
Brachydactyly with anonychia (Cooks syndrome)	AD	*KCNJ2*	106995	1487	Duplications of *SOX9/KCNJ2* regulatory region
Preaxial brachydactyly, PAX3 type	AD	*PAX3*			See PMID 25959774
38. Brachydactylies (with extraskeletal manifestations)					
Brachydactyly–mental retardation syndrome	AD	*HDAC4*	600430	1001	Some patients have microdeletions involving contiguous genes (2q37 deletion syndrome)

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Hyperphosphatasia with mental retardation, brachytelephalangy, and distinct face	AR	*PIGV*	239300	247262	
Brachydactyly-hypertension syndrome (Bilginturan)	AD	*PDE3A*	112410	1276	
Microcephaly-oculo-digito-esophageal-duodenal syndrome (Feingold syndrome)	AD	*MYCN*	164280	1305	
Hand-foot-genital syndrome	AD	*HOXA13*	140000	2438	
Rubinstein–Taybi syndrome	AD AD	*CREBBP* *EP300*	180849 613684	783 353284	
Brachydactyly, Temtamy type	AR	*CHSY1*	605282	363417	
Coffin–Siris syndrome	AD AD AD AD	*ARID1B* *SMARCB1* *SMARCA4* *SMARCE1*	135900 614608 614609 616938	1465	Mutations in various components of the SWI/SNF complex have been reported in patients with a diagnosis of Coffin–Siris syndrome
Catel–Manzke syndrome	AR	*TGDS*	616145	1388	
Pseudohypoparathyroidism type IA	AD	*GNAS*	103580	79443	Caused by loss-of-function mutations on the maternal allele; formerly known as Albright hereditary osteodystrophy
See also group 15 for other conditions with brachydactyly as well as brachytelephalangic CDP (group 21).					
39. Limb hypoplasia–reduction defects group					
Ulnar-mammary syndrome	AD	*TBX3*	181450	3138	
de Lange syndrome	AD XL AD AD XL	*NIPBL* *SMC1A* *SMC3* *RAD21* *HDAC8*	122470 300590 610759 614701 300882	199	
Fanconi anemia *(see note below)*	AR	*Several*	227650	84	Several complementation groups and genes
Thrombocytopenia-absent radius (TAR)	AR	*RBM8A*	274000	3320	Deletion and common SNP on other allele that has regulatory function
Thrombocythemia with distal limb defects	AD	*THPO*	187950	329319	Distal limb defects postulated as consequence of vascular occlusions
Holt–Oram syndrome	AD	*TBX5*	142900	392	
Okihiro syndrome (Duane–radial ray anomaly)	AD	*SALL4*	607323	93293	
Cousin syndrome	AR	*TBX15*	260660	93333	
Roberts syndrome	AR	*ESCO2*	268300	3103	
Split-hand-foot malformation with long bone deficiency (SHFLD)	AD	*BHLHA9*	612576	3329	Duplication which is less than 50% penetrant and shows markedly variable expression
Tibial hemimelia	AR		275220	93322	
Tibial hemimelia-polysyndactyly-triphalangeal thumb (Werner syndrome)	AD	*SHH*	188740	988	Mutations in ZRS (limb enhancer of SHH)
Acheiropodia	AR	*SHH*	200500	931	Deletion in *LMBR1* that affects ZRS (limb enhancer of *SHH*)
Tetra-amelia	AR AR	*WNT3* *RSPO2*	273395 618021	3301	

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Gollop–Wolfgang syndrome	AD	*BHLHA9*	228250	1986	Duplications or triplications of genomic region including *BHLHA9*
Al-Awadi Raas-Rothschild limb-pelvis hypoplasia-aplasia	AR	*WNT7A*	276820	2879	
Fuhrmann syndrome	AR	*WNT7A*	228930	2854	
RAPADILINO syndrome	AR	*RECQL4*	266280	3021	
Adams–Oliver syndrome	AD AR AD AR AD AD	*ARHGAP31* *DOCK6* *RBPJ* *EOGT* *NOTCH1* *DLL4*	100300 614219 614814 615297 616028 616589	974	
Poland syndrome	SP, AD		173800	2911	
Femoral hypoplasia-unusual face syndrome (FHUFS)	SP		134780	1988	Some phenotypic overlap with FFU syndrome (below)
Fibular Aplasia, Tibial Campomelia, and Oligosyndactyly syndrome (FATCO)	SP, AD?		246570	2492	
Femur-fibula-ulna syndrome (FFU)	SP		228200	2019	
Hanhart syndrome (Hypoglossia-hypodactylia)	AD		103300	989	
Scapulo-iliac dysplasia (Kosenow)	AD		169550	2839	
Clubfoot with or without deficiency of long bones and/or mirrorimage polydactyly	AD	*PITX1*	119800	199315	In some patients bilateral patellar hypoplasia (see group 36)
Sirenomelia	SP			3169	Probably heterogeneous
Terminal transverse defects	SP		102650	973	
Note: The particularly complex genetic basis of Fanconi anemia and its complementation groups is acknowledged but not further listed in this nosology. The reader is referred to OMIM or to specialized reviews—*See also* CHILD in group 21 and the mesomelic and acromesomelic dysplasias.					
40. Ectrodactyly with and without other manifestations					
Ankyloblepharon-ectodermal dysplasia-cleft palate (AEC)	AD	*TP63*	106260	1071	
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 3 (EEC3)	AD	*TP63*	604292	1896	
Ectrodactyly-ectodermal dysplasia-macular dystrophy syndrome (EEM)	AR	*CDH3*	225280	1897	
Limb-mammary syndrome (including ADULT syndrome)	AD	*TP63*	603543	69085	
Split–hand–foot malformation, isolated form, type 4 (SHFM4)	AD	*TP63*	605289	2440	
Split–hand–foot malformation, isolated form, type 1 (SHFM1)	AD AD	*DLX5* *DLX6*	220600 183600	2440	Structural variations at locus; also regulatory mutations affecting exons of *DYNC1I1* that regulate *DLX5*
Split–hand–foot malformation, isolated form, type 3 (SHFM3)	AD	*10q24*	246560	2440	Duplications at 10q24 encompassing *LBX1*, *BTRC*, *POLL*, *DPCD*, and *FBXW4*

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Split–hand–foot malformation, isolated form, type 6 (SHFM6)	AR	*WNT10B*	225300	2440	
Split-foot malformation with mesoaxial polydactyly (SFMMP)	AR	*ZAK*	616890	488232	
Hartsfield syndrome	AD	*FGFR1*	615465	2117	
41. Polydactyly-Syndactyly-Triphalangism group					
Preaxial polydactyly type 1 (PPD1)	AD	*SHH*	174400	93339	Regulatory mutation or duplication of ZRS (limb enhancer of *SHH*)
Preaxial polydactyly type 2 (PPD2)/Triphalangeal thumb (TPT)	AD	*SHH*	174500	93336	Regulatory mutation or duplication of ZRS (limb enhancer of *SHH*)
Preaxial polydactyly type 3 (PPD3)	AD		174600	93337	
Preaxial polydactyly type 4 (PPD4)	AD	*GLI3*	174700	93338	
Greig cephalopolysyndactyly syndrome	AD	*GLI3*	175700	380	
Pallister–Hall syndrome	AD	*GLI3*	146510	672	
Synpolydactyly (complex, fibulin1—associated)	AD	*FBLN1*	608180	93403	
Synpolydactyly	AD	*HOXD13*	186000	295195	
Townes-–Brocks syndrome (renal–ear–anal–radial syndrome)	AD	*SALL1*	107480	857	
Lacrimo-auriculo-dento-digital syndrome (LADD)	AD AD AD	*FGFR2* *FGFR3* *FGF10*	149730	2363	
Acrocallosal syndrome	AR	*KIF7*	200990	36	
Acro-pectoral syndrome	AD		605967	85203	
Acro-pectoro-vertebral dysplasia (F-syndrome)	AD	*WNT6*	102510	957	Structural variations of locus resulting in ectopic activation of *WNT6*
Mirror-image polydactyly of hands and feet (Laurin-Sandrow syndrome)	AD	*SHH*	135750	2378	Duplication of ZRS (limb enhancer of *SHH*)
Cenani–Lenz syndactyly	AR	*LRP4*	212780	3258	
Cenani–Lenz like syndactyly	SP, AD?	*GREM1*, *FMN1*			Monoallelic duplication of both loci (observed in one case only so far)
Oligosyndactyly, radio-ulnar synostosis, hearing loss and renal defects syndrome	SP, AR?	*FMN1*			Deletion
Syndactyly, Malik–Percin type	AD	*BHLHA9*	609432	157801	
STAR syndrome (syndactyly of toes, telecanthus, ano- and renal malformations)	XL	*FAM58A*	300707	140952	
Syndactyly type 1 (III-IV)	AD		185900	93402	
Syndactyly type 3 (IV-V)	AD	*GJA1*	186100	93404	
Syndactyly type 4 (I-V) Haas type	AD	*SHH*	186200	93405	Duplication of ZRS (limb enhancer of *SHH*)
Syndactyly Lueken type	AD	*IHH*		295189	Duplication of *IHH* and regulatory region
Syndactyly type 5 (syndactyly with metacarpal and metatarsal fusion)	AD	*HOXD13*	186300	93406	
Syndactyly with craniosynostosis (Philadelphia type)	AD	*IHH*	185900	1527	Duplication of *IHH* regulatory region
Syndactyly with microcephaly and mental retardation (Filippi syndrome)	AR	*CKAP2L*	272440	3255	

(Continues)

TABLE 1 (Continued)

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
Meckel syndrome types 1–6	AR	*MKS1*	249000	564	
	AR	*TMEM216*	603194		
	AR	*TMEM67*	607361		
	AR	*CEP290*	611134		
	AR	*RPGRIP1L*	611561		
	AR	*CC2D2A*	612284		
Note: Smith–Lemli–Opitz syndrome can present with polydactyly and/or syndactyly. See also the Ciliopathy group 9.					
42. Defects in joint formation and synostoses					
Multiple synostoses syndrome	AD	*NOG*	186500	3237	
	AD	*GDF5*	610017		
	AD	*FGF9*	612961		
	AD	*GDF6*	617898		
Radio-ulnar synostosis with amegakaryocytic thrombocytopenia	AD	*HOXA11*	605432	71289	
	AD	*MECOM*	616738		
Liebenberg syndrome	AD	*PITX1*	186550	1275	Deletion of *H2AFY* gene resulting in ectopic activation of *PITX1* in the upper limb
SAMS syndrome	AR	*GSC*	602471	397623	
See also spondylocarpotarsal synostosis syndrome (group 7), mesomelic dysplasia with acral synostoses (group 17) and others.					

However, these conditions were considered not to meet the inclusion criteria (mainly lack of significant skeletal involvement) and were therefore not incorporated into the Nosology. Phenotypes showing locus heterogeneity but clinically and/or radiographically almost indistinguishable from each other were included as one entry in the Nosology. Examples include the autosomal dominant form of multiple epiphyseal dysplasia (group 10), microcephalic osteodysplastic primordial dwarfism (group 19), rhizomelic chondrodysplasia punctata (group 21), and the severe, infantile form of osteopetrosis (group 23). For osteogenesis imperfecta, the more phenotypically based Sillence classification was kept as in the previous revisions of the Nosology (Van Dijk & Sillence, 2014). Several new entities have been added to the SEMD group (group 13). These disorders were previously ill-defined and classified as "aspecific" or "unknown" types of SEMD. The use of exome or whole genome sequencing has solved their molecular mystery and has now rendered them the status of separate and well-defined entities within the Nosology.

4 | DISCUSSION

As with the previous revisions, the major challenge was keeping up with the rapid pace at which new entities are described and new genes are discovered. Next generation sequencing has revolutionized genetic medicine and this advance is also reflected in the field of genetic bone disorders. For many of these disorders, the molecular defect has now been identified. In this new edition of the Nosology, the causal gene or genomic alteration is listed for 92% (425/461) of the disorders. Previously, the percentages of disorders that had been "solved" genetically were 58% (215/372) for the 2006 revision, 69% (316/456) for the 2010 revision, and 88% (385/436) for the 2015 revision (Bonafe et al., 2015; Superti-Furga & Unger, 2007; Warman et al., 2011). The 2010 revision was published when the application of massively parallel sequencing to Mendelian genetic diseases was just beginning (Ng et al., 2010). Not only well-known entities, previously carefully delineated based on their clinical and/or radiographic features, are being "solved" at the genetic level, but also new disorders and their causal genes are being discovered and reported at a rather rapid pace. The latter is often the result of a "genotype first—phenotype later" approach in individuals with an "unknown" skeletal dysplasia and facilitated through web-based tools such as GeneMatcher, which enables the comparison of phenotypes among patients with pathogenic variants in a newly identified gene (Sobreira et al., 2015).

The 437 disease-causing genes listed in the 2019 Nosology are functionally diverse, involved in a broad range of cell biologic processes, and cause disease by a variety of mutational mechanisms. They not only code for tissue-specific proteins that are essential for the formation and maintenance of bone and cartilage but also encode proteins that have a more ubiquitous role such as regulating gene transcription, cell division, or intracellular transport. While many disease-causing genes have clear roles in skeletal development (e.g., those involved in NOTCH, WNT, TGFβ, or BMP signaling), the skeletal roles for other genes are not yet clear. For example,

pathogenic variants in mitochondrial proteins can cause a skeletal dysplasia, which is surprising, since skeletal manifestations are uncommon for most mitochondrial disorders (Dikoglu et al., 2015; Girisha et al., 2019; Mehawej et al., 2014; Peter et al., 2019; Royer-Bertrand et al., 2015). In addition, genes that do not encode proteins are also responsible for skeletal disorders. A well-known and longstanding example is cartilage hair hypoplasia that is caused by pathogenic variants in *RMRP*, which encodes an RNA component of the mitochondrial RNA processing endoribonuclease. Interestingly, the current Nosology now includes the first example of pathogenic variants in a miRNA causing a skeletal dysplasia (SED, MIR140 type; group 15) (Grigelioniene et al., 2019). Alterations in regulatory sequences, residing outside the genes, are another well-established cause of skeletal disorders. As a general rule, these disorders are characterized by defects in early skeletal development and patterning and tend to affect a particular set of bones in the skeleton (dysostoses). They usually do not present as true chondrodysplasias having widespread epiphyseal or metaphyseal changes. For example, pathogenic variants in an upstream cis-regulatory enhancer of the *SHH* gene (known as the ZPA regulatory sequence) can cause a spectrum of limb malformations ranging from preaxial polydactyly and triphalangeal thumb to the more severe Werner mesomelic dysplasia (Girisha et al., 2014; Wieczorek et al., 2010). Structural variations and translocations within the vicinity of the *HOXD* cluster locus on chromosome 2 have been reported in several limb malformations, including mesomelic dysplasia Kantaputra type (Kantaputra et al., 2010). Similarly, a particular deletion encompassing four protein coding genes on 6p22.3 has been identified in three unrelated patients with mesomelic dysplasia Savarirayan type (Flöttmann et al., 2015). In this paper, the authors provide evidence that haploinsufficiency for the deleted genes is not the mutational mechanism but rather the disruption of topologically associated domains in this region. By the deletion, two regulatory boundaries are removed and new limb enhancers are brought into close proximity of the *ID4* gene, a phenomenon known as enhancer adoption.

The classification and organization of disorders have not been changed significantly compared with the previous editions. The Nosology still remains "hybrid" in nature in the sense that the classification is not always based on the same criteria. Some diseases are grouped based on the causal gene, others are listed together, because they share common radiographic features, and still others are brought together because of a similar clinical course (lethality) or involvement of similar parts of the skeleton. A Web-based Nosology with a clinical, radiographic, and molecular annotation for each disorder and with links to different databases would not only solve this classification issue but would also enable more specific searches per gene, pathway, or clinical/radiographic feature.

Regular revisions of the Nosology on Skeletal Disorders are important. The Nosology can serve as a diagnostic aid for clinicians who care for individuals with a skeletal disorder. In addition, it can facilitate the recognition of new entities and be a guide in the interpretation of new genetic variants. Finally, the Nosology can foster and enhance research by providing a catalogue of genes with important roles in skeletal biology.

ACKNOWLEDGMENTS

The authors are indebted to both Manila Boarini and Marina Mordenti (IRCCS Rizzoli Orthopedic Institute, Bologna) for their help with the assignment of the Orphanet codes in Table 1. The authors also thank Andrew Jackson (MRC Institute of Genetics and Molecular Medicine, Edinburgh), Fleur van Dijk (Clinical Genetics, Northwick Park Hospital London), and Wim Van Hul (Department of Medical Genetics, University of Antwerp) for their expert advice on groups 19, 23, 24, and 25 listed in Table 1.

ORCID

Geert R. Mortier https://orcid.org/0000-0001-9871-4578
Daniel H. Cohn https://orcid.org/0000-0003-0388-4457
Stephen Robertson https://orcid.org/0000-0002-5181-7809

REFERENCES

A Nomenclature for Constitutional (Intrinsic) Diseases of Bones. (1971). *The Journal of Pediatrics*, *78*, 177–179.

Beighton, P., Giedion, A., Gorlin, R., Hall, J., Horton, B., Kozlowski, K., … Spranger, J. (1992). International classification of Osteochondrodysplasias. *American Journal of Medical Genetics*, *44*(2), 223–229. https://doi.org/10.1002/ajmg.1320440220

Bonafe, L., Cormier-Daire, V., Hall, C., Lachman, R., Mortier, G., Mundlos, S., … Unger, S. (2015). Nosology and classification of genetic skeletal disorders: 2015 revision. *American Journal of Medical Genetics. Part A*, *167*(12), 2869–2892. https://doi.org/10.1002/ajmg.a.37365

Dikoglu, E., Alfaiz, A., Gorna, M., Bertola, D., Chae, J. H., Cho, T. J., … Unger, S. (2015). Mutations in LONP1, a mitochondrial matrix protease, cause CODAS syndrome. *American Journal of Medical Genetics. Part A*, *167*(7), 1501–1509. https://doi.org/10.1002/ajmg.a.37029

Flöttmann, R., Wagner, J., Kobus, K., Curry, C. J., Savarirayan, R., Nishimura, G., … Spielmann, M. (2015). Microdeletions on 6p22.3 are associated with mesomelic dysplasia Savarirayan type. *Journal of Medical Genetics*, *52*(7), 476–483. https://doi.org/10.1136/jmedgenet-2015-103108

Girisha, K. M., Bidchol, A. M., Kamath, P. S., Shah, K. H., Mortier, G. R., Mundlos, S., & Shah, H. (2014). A novel mutation (g.106737G>T) in zone of polarizing activity regulatory sequence (ZRS) causes variable limb phenotypes in Werner mesomelia. *American Journal of Medical Genetics. Part A*, *164*(4), 898–906. https://doi.org/10.1002/ajmg.a.36367

Girisha, K. M., von Elsner, L., Neethukrishna, K., Muranjan, M., Shukla, A., Bhavani, G. S., … Mortier, G. (2019). The homozygous variant c.797G>A/p.(Cys266Tyr) in PISD is associated with a spondyloepimetaphyseal dysplasia with large epiphyses and disturbed mitochondrial function. *Human Mutation*, *40*(3), 299–309. https://doi.org/10.1002/humu.23693

Grigelioniene, G., Suzuki, H. I., Taylan, F., Mirzamohammadi, F., Borochowitz, Z. U., Ayturk, U. M., … Kobayashi, T. (2019). Gain-of-function mutation of microRNA-140 in human skeletal dysplasia. *Nature Medicine*, *25*(4), 583–590. https://doi.org/10.1038/s41591-019-0353-2

Hall, C. M. (2002). International nosology and classification of constitutional disorders of bone (2001). *American Journal of Medical Genetics*, *113*(1), 65–77. https://doi.org/10.1002/ajmg.10828

International Nomenclature and Classification of the Osteochondrodysplasias. (1998). International working group on constitutional diseases of bone. *American Journal of Medical Genetics*, *79*, 376–382.

International Nomenclature of Constitutional Bone Diseases. (1971). Constitutional bone diseases without known pathogenesis. *Archives Françaises de Pédiatrie*, *28*, 553–557.

International Nomenclature of Constitutional Diseases of Bones. (1970). *Annales de Radiologie (Paris)*, *13*, 455–464.

International Nomenclature of Constitutional Diseases of Bones: Revision, May 1977. (1979). *American Journal of Medical Genetics*, *3*, 21–26.

International Nomenclature of Constitutional Diseases of Bones: Revision, May 1983. (1983). *Annales de Radiologie (Paris)*, *26*, 457–462.

Kantaputra, P. N., Klopocki, E., Hennig, B. P., Praphanphoj, V., Le Caignec, C., Isidor, B., … Mundlos, S. (2010). Mesomelic dysplasia Kantaputra type is associated with duplications of the HOXD locus on chromosome 2q. *European Journal of Human Genetics*, *18*(12), 1310–1314. https://doi.org/10.1038/ejhg.2010.116

Lachman, R. S. (1998). International nomenclature and classification of the osteochondrodysplasias (1997). *Pediatric Radiology*, *28*(10), 737–744. https://doi.org/10.1007/s002470050458

McKusick, V. A., & Scott, C. I. (1971). A Nomenclature for Constitutional Disorders of Bones. *Journal of Bone and Joint Surgery (American)*, *53*(5), 978–986.

Mehawej, C., Delahodde, A., Legeai-Mallet, L., Delague, V., Kaci, N., Desvignes, J. P., … Mégarbané, A. (2014). The impairment of MAGMAS function in human is responsible for a severe skeletal dysplasia. *PLoS Genetics*, *10*(5), e1004311. https://doi.org/10.1371/journal.pgen.1004311

Ng, S. B., Buckingham, K. J., Lee, C., Bigham, A. W., Tabor, H. K., Dent, K. M., … Bamshad, M. J. (2010). Exome sequencing identifies the cause of a mendelian disorder. *Nature Genetics*, *42*(1), 30–35. https://doi.org/10.1038/ng.499

Peter, V. G., Quinodoz, M., Pinto-Basto, J., Sousa, S. B., Di Gioia, S. A., Soares, G., … Campos-Xavier, B. (2019). The Liberfarb syndrome, a multisystem disorder affecting eye, ear, bone, and brain development, is caused by a founder pathogenic variant in the PISD gene. *Genetics in Medicine*. https://doi.org/10.1038/s41436-019-0595-x Epub ahead of print.

Rimoin, D. L. (1997). International nomenclature of constitutional diseases of bone with bibliography. *Birth Defects: Original Article Series*, *15*, 30.

Royer-Bertrand, B., Castillo-Taucher, S., Moreno-Salinas, R., Cho, T. J., Chae, J. H., Choi, M., … Superti-Furga, A. (2015). Mutations in the heat-shock protein A9 (HSPA9) gene cause the EVEN-PLUS syndrome of congenital malformations and skeletal dysplasia. *Scientific Reports*, *5*, 17154. https://doi.org/10.1038/srep17154

Sobreira, N., Schiettecatte, F., Valle, D., & Hamosh, A. (2015). GeneMatcher: A matching tool for connecting investigators with an interest in the same gene. *Human Mutation*, *36*(10), 928–930. https://doi.org/10.1002/humu.22844

Spranger, J. (1992). International classification of osteochondrodysplasias. The international working group on constitutional diseases of bone. *European Journal of Pediatrics*, *151*(6), 407–415. https://doi.org/10.1007/bf01959352

Superti-Furga, A., & Unger, S. (2007). Nosology and classification of genetic skeletal disorders: 2006 revision. *American Journal of Medical Genetics. Part A*, *143*(1), 1–18. https://doi.org/10.1002/ajmg.a.31483

Van Dijk, F. S., & Sillence, D. O. (2014). Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. *American Journal of Medical Genetics. Part A*, *164*(6), 1470–1481. https://doi.org/10.1002/ajmg.a.36545

Warman, M. L., Cormier-Daire, V., Hall, C., Krakow, D., Lachman, R., LeMerrer, M., … Superti-Furga, A. (2011). Nosology and classification of genetic skeletal disorders: 2010 revision. *American Journal of Medical Genetics. Part A*, *155*(5), 943–968. https://doi.org/10.1002/ajmg.a.33909

Wieczorek, D., Pawlik, B., Li, Y., Akarsu, N. A., Caliebe, A., May, K. J., … Wollnik, B. (2010). A specific mutation in the distant sonic hedgehog (SHH) cis-regulator (ZRS) causes Werner mesomelic syndrome (WMS) while complete ZRS duplications underlie Haas type polysyndactyly and preaxial polydactyly (PPD) with or without triphalangeal thumb. *Human Mutation*, *31*(1), 81–89. https://doi.org/10.1002/humu.21142

How to cite this article: Mortier GR, Cohn DH, Cormier-Daire V, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. *Am J Med Genet Part A*. 2019;179A: 2393–2419. https://doi.org/10.1002/ajmg.a.61366