Nosology and Classification of Genetic Skeletal Disorders: 2019 Revision

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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.

KEY WORDS

nosology, skeletal dysplasias, dysostoses, skeletal genetics, skeletal malformation syndromes

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 Bone (1970; 1971a; 1971b; McKusick & Scott, 1971). The goal was to reach an agreement on the nomenclature of several genetic skeletal disorders that were reported since the early sixties. 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 (1979; 1983; 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.

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. Silience, 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 following: DC to groups 2,3,6,7,8,10; VCD to groups 1,9,15,20,30; CH to groups 23,24,32,33,36; DK to groups 7,9; GM to groups 2,3,10,16,28,30,35; SM to groups 37-42; GN to groups 13,18,19,21,26,28,34,36; SR to group 7; LS to groups 25,29; RS to groups 1,17,19,33; DS to groups 22-27; ASF to groups 4,11,12,20,31,35; SU to groups 5,8,10,14,22 and MW to groups 3,16,29. 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: i) the disorder should have significant skeletal involvement, corresponding to the definition of either skeletal dysplasias/dysostoses, metabolic bone disorders, or skeletal malformation/reduction syndromes; ii) the disorder should have achieved peer-reviewed publication status with listing in PubMed, OMIM or another biomedical archive/database; iii) 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); iv) the disorder should have nosologic autonomy, i.e. 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 (HGNC). 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.

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 1,2,5,6,8) and one phenotype can be caused by variants in several genes (e.g., groups 9,25). Pathogenic variants in *FGFR3*, *COL2A1*, *COMP*, *NPR2* and *ACAN* can cause mild phenotypes such as isolated short stature or premature degenerative joint disease. 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.

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, 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 do 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. Whereas many disease-causing genes have clear roles in skeletal development (e.g., those involved in NOTCH, WNT, TGF β 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; Wiczorek 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 has not been changed significantly compared to 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.

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Legend to Table 1 (Table in separate file):

Table 1 lists the 461 skeletal disorders classified into 42 groups. For each disorder, the inheritance pattern and causal gene (if known) is 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”.

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<u>Group / Name of Disorder</u>	<u>Inheritance</u>	<u>Gene(s)</u>	<u>OMIM number</u>	<u>ORPHANET code</u>	<u>Notes</u>
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 SED with premature onset arthrosis and SED Stanescu type. Mild SED cases may resemble MED (see note). AR*: A few cases with bi-allelic 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, dyssspondyloenchondromatosis 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, 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					
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 (non-ocular)	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: <i>HSPG2</i> 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
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 spondylohumero-femoral (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 non-lethal 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 (acrofacial) 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	DYNC2H1	613091	474	Dynein motor
	AR	DYNC2LI1			
	AR	WDR34			
	AR	TCTEX1D2			
	AR	WDR60			
	AR	WDR19			Retrograde transport (IFT-A)
	AR	IFT140			
	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 <i>INTU</i>, <i>CEP120</i> and <i>C2CD3</i>
Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1, 2	AR	IFT122	218330	1515	
	AR	WDR35			
	AR	WDR19			
	AR	IFT43			
	AR	IFT52			

Mainzer-Saldino syndrome	AR AR	IFT140 IFT172	266920	140969	
Axial spondylometaphyseal dysplasia	AR AR	CFAP410 NEK1	602271	168549	
Thoracolumbar 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 AD AD AD AD	COMP COL9A2 COL9A3 MATN3 COL9A1	132400 600204 600969 607078 614135	93308 166002 166002 93311 166002	Not all MED (-like) cases seem to have mutations in these genes
Stickler syndrome, recessive type	AR AR AR	COL9A1 COL9A2 COL9A3	614134 614284 120270	250984	See also groups 2 and 3
See also multiple epiphyseal dysplasia, recessive type in groups 4 and 20 as well as ASPED in group 15					
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	DDRKG1	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)
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	

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)
Angel-shaped phalango-epiphyseal dysplasia (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 rhizomesomelic 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
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 SLC05A1	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
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-Hünemann 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

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 auto-immune 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 non-lethal forms)	AR	FAM20C	259775	1832	Includes lethal and non-lethal 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 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	
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-osteoarthritis and cases of recessive pachydermoperiostosis
Pachydermoperiostosis (hypertrophic osteoarthropathy, primary, autosomal dominant)	AD		167100	2796	Relationship to recessive form (OMIM 259100, HPGD deficiency) unclear
Oculodontoosseous dysplasia (ODOD) mild type	AD	GJA1	164200	2710	
Oculodontoosseous dysplasia (ODOD) severe type	AR	GJA1	257850	2710	Possibly homozygous form of mild ODOD
Osteoectasia with hyperphosphatemia (juvenile Paget disease)	AR	OPG	239000	2801	
Osteosclerosis	AD	LRP5	144750	2790 2783 3416	Includes AD osteopetrosis type 1 (OPTA1) (MIM 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
Trichodontoosseous 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
Cranioimetadiaphyseal 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, non-deforming 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	-
	XL	MBTPS2	301014		OMIM OI type XIX
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, arthrogyrosis and BS1 documented
Bruck syndrome type 2 (BS2)	AR	PLOD2	609220	2771	
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	CDC73	145000	99879	Genetic hyperparathyroidism due to parathyroid adenoma occurs in a number of tumor-associated syndromes such as MEN
	AD	CDC73	145001	99880	
	AD	-	610071	99879	
	AD	GCM2	617343	99879	
Neonatal hyperparathyroidism, severe form	AR, AD	CASR	239200	417	
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 <i>FAM20C</i> 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	
Mucopolidosis II (I-cell disease), alpha/beta type	AR	GNPTAB	252500	576	
Mucopolidosis III (Pseudo-Hurler polydystrophy), alpha/beta type	AR	GNPTAB	252600	423461	
Mucopolidosis III (Pseudo-Hurler polydystrophy), gamma type	AR	GNPTG	252605	423470	
Other conditions resembling storage diseases: congenital disorders of glycosylation and geleophysic dysplasia (group 15)					
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 angiomas 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					
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	NFI	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	TGFB1 TGFB2 , 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 <i>NPPC</i>
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)

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 gyrate (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), osteocraniosynostosis (group 19), Cole-Carpenter syndrome (group 25), CDAGS syndrome (group 32), and 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)					
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 (acrofacial) dysostosis	AD AD	EVC1 EVC2	193530	952	See also ciliopathy 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)

[illegible]

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)

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 syndrome1	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 brachytelephalangi 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	
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 DYNC111 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
Split hand-foot malformation, isolated form, type 6 (SHFM6)	AR	WNT10B	225300	2440	
Split-foot malformation with mesoaxial polydactyly (SFMM6)	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	

Meckel syndrome type 1,2,3,4,5,6	AR AR AR AR AR AR	MKS1 TMEM216 TMEM67 CEP290 RPGRIP1L CC2D2A	249000 603194 607361 611134 611561 612284	564	
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 AD AD AD	NOG GDF5 FGF9 GDF6	186500 610017 612961 617898	3237	
Radio-ulnar synostosis with amegakaryocytic thrombocytopenia	AD AD	HOXA11 MECOM	605432 616738	71289	
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.

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