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Nosology and Classification of Genetic Skeletal Disorders: 2006 Revision

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The objective of the paper is to provide the revision of the Nosology of Constitutional Disorders of Bone that incorporates newly recognized disorders and reflects new molecular and pathogenetic concepts. Criteria for inclusion of disorders were (1) significant skeletal involvement corresponding to the definition of skeletal dysplasias, metabolic bone disorders, dysostoses, and skeletal malformation and/or reduction syndromes, (2) publication and/or MIM listing, (3) genetic basis proven or very likely, and (4) nosologic autonomy confirmed by molecular or linkage analysis and/or distinctive diagnostic features and observation in multiple individuals or families. Three hundred seventy-two different conditions were included and placed in 37 groups defined by molecular, biochemical and/or radiographic criteria. Of these conditions, 215 were associated with one or more of 140 different genes. Nosologic status was classified as final (mutations or locus identified), probable (pedigree evidence), or *bona fide* (multiple observations and clear diagnostic criteria, but no pedigree or locus evidence yet). The number of recognized genetic disorders with a significant skeletal component is growing and the distinction between dysplasias, metabolic bone disorders, dysostoses, and malformation syndromes is blurring. For classification purposes, pathogenetic and molecular criteria are integrating with morphological ones but disorders are still identified by clinical features and radiographic appearance. Molecular evidence leads to confirmation of individual entities and to the constitution of new groups, but also allows for delineation of related but distinct entities and indicates a previously unexpected heterogeneity of molecular mechanisms; thus, molecular evidence does not necessarily simplify the Nosology, and a further increase in the number of entities and growing complexity is expected. By providing an updated overview of recognized entities with skeletal involvement and of the underlying gene defects, the new Nosology can provide practical diagnostic help, facilitate the recognition of new entities, and foster and direct research in skeletal biology and genetic disorders. © 2006 Wiley-Liss, Inc.

Key words: nosology; skeletal disorders; osteochondrodysplasias; dysostoses; malformation syndromes; developmental biology; molecular defects

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INTRODUCTION

Following the discovery on numeric chromosomal aberrations medical genetics experienced a historical boost in the early 1960s, culminating in the Birth Defects Conferences. Shortly thereafter, the accumulating evidence of the great heterogeneity of genetic skeletal disorders prompted a group of experts from various countries to prepare a document to reach an agreement on the nomenclature of what was then called "Constitutional (or Intrinsic) Disorders of Bone" [INCDB, 1970; NCDB, 1971a,b; McKusick and Scott, 1971]. The "Nomenclature" was meant to bring together experts in radiology, clinical genetics and pediatrics to agree on the denomination and classification of the skeletal disorders, syndromes and metabolic diseases that were being described at a rapid pace. Much has changed since the first Nomenclature was published in 1970. Revision has been prepared in 1977, 1983, 1992, 1997, and 2001 [INCDB, 1978, 1983; INCO, 1998; Hall, 2002]. Electronic means have tremendously accelerated the pace at which new observations and results can be made public; knowledge on the molecular basis of disorders has increased to the point that the causative gene is known for approximately one-half of the close to 400 disorders included today. Because of the wealth of available data on the clinical and radiographic features, inheritance pattern, and—in many cases—the molecular basis, the determination of nomenclature name and classification of each disorder should now be called "nosology," while the term "constitutional" can be replaced with "genetic." Following the establishment of the International Skeletal Dysplasia Society in 1999, and to cope with the increasing complexity of information, revisions of the Nosology have been delegated to an expert group nominated ad hoc within the ISDS to guarantee balanced representation of clinical, radiological and molecular expertise.

METHODS

The Nosology Group of the International Skeletal Dysplasia Society met in August 2005 to revise the 2001 edition of the Nosology [Hall, 2002]. In the preceding months, curators (usually two to three for every group of disorders) had been appointed who were responsible for reviewing the recent literature and discussing possible changes ahead of the meeting. During the meeting, a consensus was reached for changes to be made, and the drafts were circulated for correction after the meeting. The criteria used for inclusion of individual disorders were:

(1) significant skeletal involvement, corresponding to the definition of skeletal dysplasias, metabolic bone disorders, dysostoses, and skeletal malformation and/or reduction syndromes,
(2) publication and/or listing in OMIM (meaning that observations should not find their way into the Nosology before they achieve peer-reviewed publication status),
(3) genetic basis proven by pedigree or very likely based on homogeneity of phenotype in unrelated families,
(4) nosologic autonomy confirmed by molecular or linkage analysis and/or distinctive diagnostic features and observation in multiple individuals or families.

RESULTS

Three hundred seventy-two different conditions were included and placed in 37 groups defined by molecular, biochemical and/or radiographic criteria. Of these conditions, 215 were associated with one or more of 140 different genes. Nosologic status was classified as final (mutations or locus identified), probable (pedigree evidence), or *bona fide* (multiple observations and clear diagnostic criteria, but no pedigree or locus evidence yet). The results are presented in Table I. Within a group, disorders with known molecular basis have been listed preceding those with lesser degree of evidence; however, variants of the same disorder have been kept together. The Table I features direct links to OMIM entries.

DISCUSSION

The first criterion, the definition of "significant skeletal involvement," leaves some degree of subjectivity. The 2001 revision of the Nosology began to include more dysostoses, and the present revision goes much farther in including disorders such as dysostoses or malformation syndromes that have a skeletal component. The MIM catalogue contains many entries that include some degree of skeletal involvement, and the decision on inclusion or exclusion on the basis of what is "significant" involvement can be arbitrary.

Similar considerations apply to criterion number 4—"nosologic autonomy." Is the disorder in question an independent nosologic entity or perhaps a variant of some already existing entity? Are the diagnostic criteria specific enough to ensure accurate diagnosis? Can a genetic basis be assumed with reasonable confidence? Particularly among the disorders that have not yet benefited from molecular confirmation, the nosologic autonomy remains subject to a degree of arbitrariness. For these disorders, discussion within the Nosology group, where individual opinions can be harmonized and, if needed, corrected by the collective expertise, is of paramount importance. There are a relatively large

TABLE I. 2006 Revision of the Nosology and Classification of Genetic Disorders of Bone

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
1. FGFR3 group							
Thanatophoric dysplasia type 1 (TD1)	AD	187600	4p16.3	FGFR3	FGFR3	134934	Includes previous San Diego type
Thanatophoric dysplasia type 2 (TD2)	AD	187601	4p16.3	FGFR3	FGFR3	134934	
SADDAN (severe achondroplasia-developmental delay-acanthosis nigricans)	AD	See 134934	4p16.3	FGFR3	FGFR3	134934	
Achondroplasia	AD	100800	4p16.3	FGFR3	FGFR3	134934	
Hypochondroplasia	AD	146000	4p16.3	FGFR3	FGFR3	134934	
Hypochondroplasia-like dysplasia	AD, SP						Similar to hypochondroplasia but unlinked to FGFR3, probably heterogeneous
See also Group 30 for craniosynostoses syndromes linked to FGFR3 mutations; LADD in Group 36 for another FGFR3-related phenotype; and Torrance dysplasia (Group 2) and the severe spondylodysplastic dysplasias (Group 12) for the differential diagnosis of TD1 and TD2.							
2. Type 2 collagen group							
Achondrogenesis type 2 (ACG2; Langer-Saldino)	AD	200610	12q13.1	COL2A1	Type 2 collagen	120140	
Platyspondylic dysplasia, torrance type	AD	151210 (erroneous)	12q13.1	COL2A1	Type 2 collagen	120140	See also Severe Spondylodysplastic dysplasias (Group 13)
Hypochondrogenesis	AD	200610	12q13.1	COL2A1	Type 2 collagen	120140	
Spondyloepiphyseal dysplasia congenital (SEDC)	AD	183900	12q13.1	COL2A1	Type 2 collagen	120140	
Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type	AD	184250	12q13.1	COL2A1	Type 2 collagen	120140	
Kniest dysplasia	AD	156550	12q13.1	COL2A1	Type 2 collagen	120140	
Spondyloperipheral dysplasia	AD	271700	12q13.1	COL2A1	Type 2 collagen	120140	
Mild SED with premature onset arthrosis	AD		12q13.1	COL2A1	Type 2 collagen	120140	Includes SED Namaqualand type
Stickler syndrome type 1	AD	108300	12q13.1	COL2A1	Type 2 collagen	120140	
Stickler-like syndrome							Unlinked to either COL2A1, COL11A1 or COL11A2
3. Type 11 collagen group							
Stickler syndrome type 2	AD	604841	1p21	COL11A1	Type 11 collagen alpha-1 chain	120280	
Marshall syndrome	AD	154780	1p21	COL11A1	Type 11 collagen alpha-1 chain	120280	
Otospondylomegaepiphyseal dysplasia (OSMED), recessive type	AR	215150	6p21.3	COL11A2	Type 11 collagen alpha-2 chain	120290	
Otospondylomegaepiphyseal dysplasia (OSMED), dominant type (Weissenbacher–Zweymüller syndrome, Stickler syndrome type 3)	AD	215150	6p21.3	COL11A2	Type 11 collagen alpha-2 chain	120290	
See also Stickler syndrome type 1 in Group 2							
4. Sulphation disorders group							
Achondrogenesis type 1B (ACG1B)	AR	600972	5q32-33	DTDST	SLC26A2 sulfate transporter	606718	
Atelosteogenesis type 2 (AO2)	AR	256050	5q32-33	DTDST	SLC26A2 sulfate transporter	606718	Includes de la Chapelle dysplasia and McAlister dysplasia

(*Continued*)

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TABLE I. (*Continued*)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
Diastrophic dysplasia (DTD)	AR	222600	5q32-33	DTDST	SLC26A2 sulfate transporter	606718	
MED, autosomal recessive type (rMED; EDM4)	AR	226900	5q32-33	DTDST	SLC26A2 sulfate transporter	606718	See also multiple epiphyseal dysplasias and pseudoachondroplasia Group (Group 9)
SEMD Omani type	AR	608637	10q22.1	CHST3	Chondroitin 6-sulfotransferase	603799	See also SEMD Group (Group 11)
SEMD Pakistani type	AR	603005	10q23-q24	PAPSS2	PAPS-Synthetase 2	603005	See also SEMD Group (Group 11)
5. Perlecan group							
Dyssegmental dysplasia, Silverman-Handmaker type	AR	224410	1q36-34	PLC (HSPG2)	Perlecan	142461	Relationship to dyssegmental dysplasia, Rolland-Desbuquois type (Group 11) unclear
Schwartz–Jampel syndrome (myotonic chondrodystrophy)	AR	255800	1q36-34	PLC (HSPG2)	Perlecan	142461	Includes previous Burton dysplasia
6. Filamin group							
Frontometaphyseal dysplasia	XLD	305620	Xq28	FLNA	Filamin A	300017	
Osteodysplasty Melnick-Needles	XLD	309350	Xq28	FLNA	Filamin A	300017	
Otopalatodigital syndrome type 1 (OPD1)	XLD	311300	Xq28	FLNA	Filamin A	300017	
Otopalatodigital syndrome type 2 (OPD2)	XLD	304120	Xq28	FLNA	Filamin A	300017	
Atelosteogenesis type 1 (AO1)	AD	108720	3p14.3	FLNB	Filamin B	603381	Includes Boomerang dysplasia, Piepkorn dysplasia, and spondylohumerofemoral (giant cell) dysplasia
Atelosteogenesis type 3 (AO3)	AD	108721	3p14.3	FLNB	Filamin B	603381	
Larsen syndrome	AD	150250	3p14.3	FLNB	Filamin B	603381	
Spondylo-carpal-tarsal dysplasia	AR	272460	3p14.3	FLNB	Filamin B	603381	
7. Short-rib dysplasia (with or without polydactyly) group							
Chondroectodermal dysplasia (Ellis-van Creveld)	AR	225500	4p16 4p16	EVC1 EVC2	EvC gene 1 EvC gene 2	604831 607261	
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	AR	263510					
SRP type 2 (Majewski)	AR	263520					
SRP type 4 (Beemer)	AR	269860					
Oral-Facial-Digital syndrome type 4 (Mohr-Majewski)	AR	258860					
Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	208500					
Thoracolaryngopelvic dysplasia (Barnes)	AD	187760					
8. Multiple epiphyseal dysplasia and pseudoachondroplasia group							
Pseudoachondroplasia (PSACH)	AD	177170	19p12-13.1	COMP	COMP	600310	
Multiple epiphyseal dysplasia (MED) type 1 (EDM1)	AD	132400	19p13.1	COMP	COMP	600310	
Multiple epiphyseal dysplasia (MED) type 2 (EDM2)	AD	600204	1p32.2-33	COL9A2	Collagen 9 alpha-2 chain	120260	
Multiple epiphyseal dysplasia (MED) type 3 (EDM3)	AD	600969	20q13.3	COL9A3	Collagen 9 alpha-3 chain	120270	

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Multiple epiphyseal dysplasia (MED) type 5 (EDM5)	AD	607078	2p23-24	MATN3	Matrilin 3	602109	
Multiple epiphyseal dysplasia (MED) type 6 (EDM6)	AD	120210	6q13	COL9A1	Collagen 9 alpha-1 chain	120210	
Multiple epiphyseal dysplasia (MED), other types							Some MED cases unlinked to known genes
Familial hip dysplasia (Beukes)	AD	142669	4q35				
See also multiple epiphyseal dysplasia, recessive type (rMED; EDM4) in sulphation disorders (Group 4)							
9. Metaphyseal dysplasias							
Metaphyseal dysplasia, Schmid type (MCS)	AD	156500	6q21-22.3	COL10A1	Collagen 10 alpha-1 chain	120110	
Cartilage-hair-hypoplasia (CHH; metaphyseal dysplasia, McKusick type)	AR	250250	9p13	RMRP	RNA component of RNAse H	157660	Includes Anauxetic dysplasia
Metaphyseal dysplasia, Jansen type	AD	156400	3p22-21.1	PTHR1	PTH/PTHrP receptor 1	168468	Activating mutations—see also: Eiken dysplasia in Group 25
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman–Bodian–Diamond syndrome, SBDS)	AR	260400	7q11	SBDS	SBDS gene, function still unclear	607444	
Metaphyseal anadysplasia	AD	309645		MMP13	Matrix metalloproteinase 13	600108	See also SEMD Missouri type in Group 11
Chronic infantile neurologic cutaneous articular syndrome (CINCA)/neonatal onset multisystem inflammatory disease (NOMID)	AD	607115	1q44	CIAS1	Cryopyrin	606416	
Metaphyseal dysplasia, Spahr type	AR	250400					
Metaphyseal acroscyphodysplasia (various types)	AR	250215					
10. Spondylometaphyseal dysplasias (SMD)							
Spondylometaphyseal dysplasia Kozlowski type	AD	184252					
Spondylometaphyseal dysplasia, Sutcliffe/corner fracture type	AD	184255					
SMD with severe genu valgum	AD	184253					Includes SMD Schmidt type and SMD Algerian type
SMD with cone-rod dystrophy	AR	608940					
See also disorders in Group 11 as well as SMD Sedaghatian type in Group 12							
11. Spondylo-epi(-meta)physeal dysplasias (SE(M)D)							
Dyggve-Melchior-Clausen dysplasia (DMC)	AR	223800	18q12-21.1	DYM	Dymeclin	607461	Includes Smith-McCort dysplasia
Immuno-osseous dysplasia (Schimke)	AR	242900	2q34-36	SMARCAL1	SWI/SNF-related regulator of chromatin subfamily A-like protein 1	606622	
Progressive pseudorheumatoid dysplasia (PPRD)	AR	208230	6q22-23	WISP3	WNT1-inducible signaling pathway protein 3	603400	
SED Kimberley type	AD	608361	15q26.1	AGC1	Aggrecan core protein	155760	
SED Wolcott-Rallison type	AR	226980	2p12	EIF2AK3	Translation initiation factor 2-alpha kinase-3	604032	
SEMD Matrilin type	AR	608728	2p23-p24	MATN3	Matrilin 3	602109	See also matrilin-related MED in Group 8
SEMD Missouri type	AD	602111	11q22.3	MMP13	Matrix metalloproteinase 13	600108	See also Metaphyseal Anadysplasia in Group 9
Metatropic dysplasia (various forms)	AD/AR	156530					
SED tarda, X-linked (SED-XL)	XLR	313400	Xp22	SEDL	Sedlin	300202	

(*Continued*)

TABLE I. (*Continued*)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
Dyssegmental dysplasia, Rolland-Desbuquois type	AR	224400					Unclear whether related to perlecan or not
SPONASTRIME dysplasia	AR	271510					
SEMD Maroteaux type (pseudo-Morquio type 2)	AR	184095					
SEMD short limb—abnormal calcification type	AR	271665					See also other dysplasias with stippling in Group 20
SEMD with joint laxity (SEMD-JL) Beighton type	AR	271640					
SEMD with joint laxity (SEMD-JL) leptodactylic or Hall type	AD	603546					
SEMD Handigodu type	AD						Includes Mseleni joint disease
Late onset SED, recessive type	AR						
See also: Opsismodysplasia (Group 14), SEMDs (Group 11), mucopolysaccharidosis type 4 (Morquio syndrome) and other conditions in Group 26							
12. Severe spondylodysplastic dysplasias							
Achondrogenesis type 1A (ACG1A)	AR	200600					
SMD Sedaghatian type	AR	250220					
Opsismodysplasia	AR	258480					
Fibrochondrogenesis	AR	228520					
Schneckenbecken dysplasia	AR	269250					
See also: Thanatophoric dysplasia, types 1 and 2 (Group 1); Achondrogenesis type 1B (ACG1B, Group 4), ACG2 and Torrance dysplasia (Group 2)							
13. Moderate spondylodysplastic dysplasias (brachyolmias)							
Brachyolmia, Hobaek/Toledo types	AR	271530 271630					
Brachyolmia, autosomal dominant type	AD	113500					
See also SED tarda (SED-XL) and late-onset recessive SED (both in Group 11)							
14. Acromelic dysplasias							
Trichorhinophalangeal dysplasia types 1/3	AD	190350 190351	8q24	TRPS1	Zinc finger transcription factor	604386	
Trichorhinophalangeal dysplasia type 2 (Langer-Giedion)	AD	150230	8q24	TRPS1	Zinc finger transcription factor	604386	Microdeletion syndrome; see also Multiple Cartilagineous Exostoses in Group 28
				EXT1	Exostosin 1	608177	
Acrocapitofemoral dysplasia	AR	607778	2q33-q35	IHH	Indian hedgehog	600726	
Angel-shaped phalangoepiphyseal dysplasia (ASPED)	AD	105835	20q11.2	GDF5	Growth and differentiation factor 5	601146	See also Brachydactyly type C (Group 34)
Weill–Marchesani syndrome, recessive type	AR	277600	19p13	ADAMTS10	Metalloproteinase with thrombospondin-like repeats	608990	
Weill–Marchesani syndrome, dominant type	AD	608328	15q21.1	FBN1	Fibrillin 1	134797	See also Shprintzen-Goldberg syndrome (Group 30)

Brachydactyly–Hypertension syndrome (Bilginturian)	AD	112410	12p12.2-11.2				
Acrodysostosis	AD	101800					
Acrolaryngeal dysplasia	AD						
Acromicric dysplasia	AD?	102370					
Cranioectodermal dysplasia (Sensenbrenner)	AR	218330					
Craniofacial conodysplasia	AD						
Familial digital arthropathy with brachydactyly	AD	606835					
Geleophysic dysplasia	AD?	231050					
Saldino-Mainzer dysplasia	AR	266920					
See also Short rib dysplasias (Group 7)							
15. Acromesomelic dysplasias							
Acromesomelic dysplasia type Maroteaux	AR	602875	9p13-12	NPR2	Natriuretic peptide receptor 2	108961	
Grebe dysplasia	AR	200700	20q11.2	GDF5	Growth and differentiation factor 5	601146	Includes acromesomelic dysplasia Hunter-Thompson type; see also Brachydactylies (Group 34)
Fibular hypoplasia and complex brachydactyly (Du Pan)	AR	228900	20q11.2	GDF5	Growth and Differentiation factor 5	601146	see also Brachydactylies (Group 34)
Acromesomelic dysplasia with genital anomalies	AR	609441	4q23-24	BMPR1B	Bone morphogenetic protein receptor 1B	603248	
Acromesomelic dysplasia, Osebold-Remondini type	AD	112910					
16. Mesomelic and rhizo-mesomelic dysplasias							
Dyschondrosteosis (Leri-Weill)	Pseudo-AD	127300	Xpter-p22.32 (pseudo-autosomal)	SHOX	Short stature—homeobox gene	312865	Includes Reinhardt-Pfeiffer dysplasia, MIM 191400
Langer type (homozygous dyschondrosteosis)	Pseudo-AR	249700	Xpter-p22.32 (pseudo-autosomal)	SHOX	Short stature—homeobox gene	312865	
Robinow syndrome, recessive type	AR	268310	9q22	ROR2	Receptor tyrosine kinase-like orphan receptor 2	602337	Includes previous COVESDEM (costo-vertebral segmentation defect with mesomelia); see also brachydactyly type B, Group 34
Robinow syndrome, dominant type	AD	180700					
Mesomelic dysplasia, Kantaputra type	AD	156232	2q24-32				
Mesomelic dysplasia, Nievergelt type	AD	163400					
Mesomelic dysplasia, Kozlowski-Reardon type	AR	249710					
Mesomelic dysplasia with acral synostoses (Verloes-David-Pfeiffer type)	AD	600383					
Mesomelic dysplasia, Savarirayan type (Triangular Tibia-Fibular Aplasia)	SP	605274					Possibly related to Nievergelt dysplasia
Omodysplasia, dominant type	AD	164745					
Omodysplasia, recessive type	AR	108721					
17. Bent bones dysplasias							
Campomelic dysplasia (CD)	AD	114290	17q24.3-25.1	SOX9	SRY-box 9	211970	Includes acampomelic campomelic dysplasia (ACD) as well as mild campomelic dysplasia (MIM 602196)
Stüve-Wiedemann dysplasia	AR	601559	5p13.1	LIFR	Leukemia inhibitory factor receptor	151443	Includes formerly neonatal Schwartz-Jampel syndrome or SJS type 2

(*Continued*)

TABLE I. (*Continued*)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
Cumming syndrome		211890					syndromal status uncertain
Kyphomelic dysplasia, several forms		211350					probably heterogeneous
Bent bones at birth can be seen in a variety of conditions, including Antley-Bixler syndrome, cartilage-hair hypoplasia, hypophosphatasia, osteogenesis imperfecta, dyssegmental dysplasia, and others							
18. Slender bone dysplasia Group							
3M syndrome	AR	273750	6p21.1	CUL7	Cullin 7	609577	
Kenny-Caffey dysplasia type 1	AR	244460	1q42-q43	TBCE	tubulin-specific chaperone E	604934	
Kenny-Caffey dysplasia type 2	AD	127000					
Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1)	AR	210710					Includes Taybi-Linder cephaloskeletal dysplasia
Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type)	AR	210720					
Microcephalic osteodysplastic dysplasia, Saul-Wilson type	AR						
IMAGE syndrome (Intrauterine Growth Retardation, Metaphyseal Dysplasia, Adrenal Hypoplasia, and Genital Anomalies)	XLR	300290	Chr. X				
Osteocraniostenosis	SP	602361					
19. Dysplasias with multiple joint dislocations							
Desbuquois dysplasia	AR	251450	17q25.3				
Recessive Larsen-like syndrome	AR	245600					Includes La Reunion Island dysplasia
Pseudodiastrophic dysplasia	AR	264180					
See also: Atelosteogenesis type 3 and Larsen syndrome (Group 6); SEMDs with joint laxity (Group 11)							
20. Chondrodysplasia punctata (CDP) Group							
CDP Conradi-Hünermann type (CDPX2)	XLD	302960	Xp11	EBP	Emopamil-binding protein	300205	
CDP X-linked recessive, brachytelephalangic type (CDPX1)	XLR	302950	Xp22.3	ARSE	Arylsulfatase E	300180	
CHILD (congenital hemidysplasia, icthyosis, limb defects)	XLD	308050	Xp11	NSDHL	NAD(P)H steroid dehydrogenase-like protein	300275	
CHILD (congenital hemidysplasia, icthyosis, limb defects)	XLD	308050	Xq28	EBP	Emopamil-binding protein	300205	
Greenberg dysplasia	AR	215140	1q42.1	LBR	Lamin B receptor, 3-beta-hydroxysterol delta (14)-reductase	600024	Includes hydrops-ectopic calcification-moth-eaten appearance dysplasia (HEM)
Rhizomelic CDP type 1	AR	215100	6q22-24	PEX7	Peroxysomal PTS2 receptor	601757	
Rhizomelic CDP type 2	AR	222765	1q42	DHPAT	Dihydroxyacetonephosphate acyltransferase (DHAPAT)	602744	
Rhizomelic CDP type 3	AR	600121	2q31	AGPS	Alkylglycerone-phosphate synthase (AGPS)	603051	
Astley-Kendall dysplasia	SP						
CDP tibial-metacarpal type	AD	118651					

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Dappled diaphyseal dysplasia	AR						Possibly identical to Greenberg dysplasia
See also SEMD short limb—abnormal calcification type in Group 11. Stippling can occur in several syndromes such as Zellweger, Smith-Lemli-Opitz and others							
21. Neonatal osteosclerotic dysplasias							
Blomstrand dysplasia	AR	215045	3p22-21.1	PTHR1	PTH/PTHrP receptor 1	168468	Caused by recessive inactivating mutations; see also Eiken dysplasia (Group 25) and Jansen dysplasia (Group 9)
Desmosterolosis	AR	602398	1p33-31.1	DHCR24	3-beta-hydroxysterol delta-24-reductase	606418	See also other sterol-metabolism related conditions in Group 20
Caffey disease (including infantile and attenuated forms)	AD	114000	17q21-22	COL1A1	Collagen 1, alpha-1 chain	120150	See also the various forms of osteogenesis imperfecta related to collagen 1 genes (Group 24)
Caffey disease (severe variants with prenatal onset)	AR	114000					
Raine dysplasia	AR	259775					
See also Astley-Kendall dysplasia in Group 20							
22. Increased bone density group (without modification of bone shape)							
Osteopetrosis, severe neonatal or infantile forms	AR	259700	11q13	TCIRG1	Subunit of ATPase proton pump	604592	
	AR		16p13	CLCN7	Chloride channel	602727	
	AR		6q21	GL(OSTM1)	Osteopetrosis associated transmembrane protein	607649	
Osteopetrosis, intermediate form	AR	259710	16p13	CLCN7	Chloride channel pump	602727	
Osteopetrosis with renal tubular acidosis	AR	259730	8q22	CA1	Carbonic anhydrase 1	114800	
Osteopetrosis, late-onset form type 1	AD	166600	11q13.4	LRP5	Low density lipoprotein receptor-related protein 5	603506	Includes Worth type osteosclerosis (MIM 144750)
Osteopetrosis, late-onset form type 2	AD	166600	16p13	CLCN7	Chloride channel pump	602727	
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	XL	300301	Xq28	IKBKG (NEMO)	Inhibitor of kappa light polypeptide gene enhancer, kinase of	300301	
Pyknodysostosis	AR	265800	1q21	CTSK	Cathepsin K	601105	
Osteopoikilosis	AD	155950	12q14	LEMD3	LEM domain-containing 3	607844	Includes Buschke-Ollendorff syndrome (MIM 166700)
Melorheostosis with osteopoikilosis	AD	155950	12q14	LEMD3	LEM domain-containing 3	607844	Includes mixed sclerosing bone dysplasia
Melorheostosis							no germline LEMD3 mutations identified so far
Dysosteosclerosis	AR	224300					
Osteomesopyknosis	AD	166450					
Osteopathia striata with cranial sclerosis	XLD	166500					
Osteopetrosis with infantile neuroaxonal dysplasia	AR?	600329					
Osteosclerosis, Stanescu type	AD	122900					

(*Continued*)

TABLE I. (*Continued*)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
23. Increased bone density group with metaphyseal and/or diaphyseal involvement							
Craniometaphyseal dysplasia, autosomal dominant type	AD	123000	5p15.2-14.2	ANKH	Homolog of mouse ANK (ankylosis) gene	605145	
Diaphyseal dysplasia Camurati-Engelmann	AD	131300	19q13	TGFbeta1	Transforming growth factor beta 1	190180	
Diaphyseal dysplasia Camurati-Engelmann, type 2							Unlinked to TGFbeta1
Oculodentoosseous dysplasia (ODOD) mild type	AD	164200	6q22-23	GJA1	Gap junction protein alpha-1	121014	
Oculodentoosseous dysplasia (ODOD) severe type	AR	257850					Possibly homozygous form of mild ODOD
Osteoectasia with hyperphosphatasia (Juvenile Paget disease)	AR	239000	8q24	OPG	Osteoprotegerin	602643	
Sclerosteosis	AR	269500	17q12-21	SOST	Sclerostin	605740	
Endosteal hyperostosis, van Buchem type	AR	239100	17q12-21	SOST	Sclerostin	605740	52 kb deletion downstream from SOST
Trichodentoosseous dysplasia	AD	190320	17q21	DLX3	Distal-less homeobox 3	600525	
Craniometaphyseal dysplasia, autosomal recessive type	AR	218400	6q21-22				
Diaphyseal medullary stenosis with bone malignancy	AD	112250	9p21-p22				
Craniodiaphyseal dysplasia	AR/AD?	218300/ 122860					
Craniometadiaphyseal dysplasia, Wormian bone type	AR						
Cranio-osteoarthropathy		259100					
Endosteal sclerosis with cerebellar hypoplasia	AR	213002					
Lenz-Majewski hyperostotic dysplasia		151050					
Metaphyseal dysplasia, Braun-Tinschert type	XL	605946					
Pachydermoperiostosis	AD/AR	167100					
Pyle disease	AR	265900					
Diaphyseal dysplasia with anemia (Ghosal)	AR	231095					Syndromic status uncertain
24. Decreased bone density group							
Osteogenesis imperfecta type 1	AD	166200	17q21-22	COL1A1	Collagen 1, alpha-1 chain	120150	
	AD	166240	7q22.1	COL1A2	Collagen 1, alpha-2 chain	120160	
Osteogenesis imperfecta type 2	AD	166210	17q21-22	COL1A1	Collagen 1, alpha-1 chain	120150	
	AD	166210	7q22.1	COL1A2	Collagen 1, alpha-2 chain	120160	
	AR	166210	3p22-p24.1	CRTAP	Cartilage-associated protein	605497	
	AR	166210	3p22-p24.1	P3H1/ LEPRE1	Prolyl 3-Hydroxylase 1 (Leprecan)	610339	
Osteogenesis imperfecta type 3	AD	259420	17q21-22	COL1A1	Collagen 1, alpha-1 chain	120150	
	AD	259420	7q22.1	COL1A2	Collagen 1, alpha-2 chain	120160	
	AR	259420	3p22-p24.1	CRTAP	Cartilage-associated protein	605497	see also Osteogenesis imperfecta type 7, below
	AR	259420	3p22-p24.1	P3H1/ LEPRE1	Prolyl 3-Hydroxylase 1 (Leprecan)	610339	
	AR	203760	7q22.1	COL1A2	Collagen 1, alpha-2 chain	120160	Extremely rare instances of recessive COL1A2 mutations giving OI at homozygosity

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Osteogenesis Imperfecta, recessive, unlinked to COL1A1 and COL1A2	AR	259440					Includes recessive OI, South African form; at present unclear whether mutations in CRTAP and P3H1/LEPRE1 account for all cases or whether further genes involved
Osteogenesis imperfecta type 4	AD	166220	17q21-22	COL1A1	Collagen 1, alpha-1 chain	120150	
	AD	166220	7q22.1	COL1A2	Collagen 1, alpha-2 chain	120160	
Osteogenesis imperfecta type 5	AD						
Osteogenesis imperfecta type 6							Nosologic dignity uncertain
Osteogenesis imperfecta type 7 (so-called "rhizomelic form")	AR		3p22-p24.1	CRTAP	Cartilage-associated protein	605497	OI type 7 described in a large Quebec kindred; see also recessive form of OI type 3, above
Osteoporosis-pseudoglioma syndrome	AR	259770	11q12-13	LRP5	LDL-receptor related protein 5	603506	
Bruck syndrome type 2 (Osteogenesis Imperfecta with pterygia)	AR	609220	3q23-24	PLOD2	Procollagen lysyl hydroxylase 2	601865	
Bruck syndrome type 1 (Osteogenesis Imperfecta with pterygia)	AR	259450	17p12				
Singleton-Merten dysplasia	AD	182250					
Geroderma osteodysplasticum	AR	231070					
Calvarial doughnut lesions with bone fragility	AD	126550					
Idiopathic juvenile osteoporosis	SP	259750					
Cole-Carpenter dysplasia (bone fragility with craniosynostosis)	SP	112240					See also craniosynostosis syndromes in Group 30
Spondylo-ocular dysplasia	AR	605822					Unlinked to collagen 1 and collagen 2 genes or to LRP5
Osteopenia with radiolucent lesions of the mandible	AD	166260					
25. Defective mineralization group							
Hypophosphatasia, perinatal lethal and infantile forms	AR	241500	1p36.1-p34	ALPL	Alkaline phosphatase, tisssue non-specific (TNSALP)	171760	
Hypophosphatasia, adult form	AD	146300	1p36.1-p34	ALPL	Alkaline phosphatase, tisssue non-specific (TNSALP)	171760	Includes odontohypophosphatasia
Hypophosphatemic rickets	XLD	307800	Xp22	PHEX	X-linked hypophosphatemia membrane protease	300550	
Hypophosphatemic rickets	AD	193100	12p13.3	FGF23	Fibroblast growth factor 23	605380	
Hypophosphatemic rickets with hypercalciuria	AR		9p	SLC34A3	Sodium-phosphate cotransporter		
Neonatal hyperparathyroidism, severe form	AR	239200	3q13.3-21	CASR	Calcium-sensing receptor	601199	
Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism	AD	145980	3q13.3-21	CASR	Calcium-sensing receptor	601199	
Eiken dysplasia	AR	600002	3p22-21.1	PTHR1	PTH/PTHrP receptor 1	168468	See also Blomstrand dysplasia (Group 21) and Metaphyseal dysplasia Jansen type (Group 9)
26. Lysosomal storage diseases with skeletal involvement (Dysostosis Multiplex Group)							
Mucopolysaccharidosis type 1H/1S	AR	607014	4p16.3	IDA	alpha-1-Iduronidase	252800	
Mucopolysaccharidosis type 2	XLR	309900	Xq27.3-28	IDS	Iduronate-2-sulfatase	309900	
Mucopolysaccharidosis type 3A	AR	252900	17q25.3	HSS	Heparan sulfate sulfatase	605270	

(*Continued*)

TABLE I. (*Continued*)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
Mucopolysaccharidosis type 3B	AR	252920	17q21	NAGLU	N-Ac-beta-D-glucosaminidase	252920	
Mucopolysaccharidosis type 3C	AR	252930	8p11-q13		Ac-CoA:alpha-glucosaminide N-acetyltransferase		
Mucopolysaccharidosis type 3D	AR	252940	12q14	GNS	N-Acetylglucosamine 6-sulfatase	607664	
Mucopolysaccharidosis type 4A	AR	253000	16q24.3	GALNS	Galactosamine-6-sulfate sulfatase	253000	
Mucopolysaccharidosis type 4B	AR	253010	3p21.33	GLBI	beta-Galactosidase	230500	
Mucopolysaccharidosis type 6	AR	253200	5q13.3	ARSB	Arylsulfatase B	253200	
Mucopolysaccharidosis type 7	AR	253220	7q21.11	GUSB	beta-Glucuronidase	253220	
Fucosidosis	AR	230000	1p34	FUCA	alpha-Fucosidase	230000	
alpha-Mannosidosis	AR	248500	19p13.2-12	MANA	alpha-Mannosidase	248500	
beta-Mannosidosis	AR	248510	4q22-25	MANB	beta-Mannosidase	609489	
Aspartylglucosaminuria	AR	208400	4q23-27	AGA	Aspartyl-glucosaminidase	208400	
GMI Gangliosidosis, several forms	AR	230500	3p21-14.2	GLB1	beta-Galactosidase	230500	
Sialidosis, several forms	AR	256550	6p21.3	NEU1	Neuraminidase (sialidase)	608272	
Sialic acid storage disease SIASD	AR	269920	6q14-q15	SLC17A5	Sialin (sialic acid transporter)	604322	
Galactosialidosis, several forms	AR	256540	20q13.1	PPGB	beta-Galactosidase protective protein	256540	
Multiple sulfatase deficiency	AR	272200	3p26	SUMF1	Sulfatase-modifying factor-1	607939	
Mucolipidosis II (I-cell disease)	AR	252500	4q21-23	GNPTA	N-Acetylglucosamine 1-phosphotransferase	607840	
Mucolipidosis III (Pseudo-Hurler polydystrophy)	AR	252600	4q21-23	GNPTA	N-Acetylglucosamine 1-phosphotransferase	607840	
27. Osteolysis group							
Familial expansile osteolysis	AD	174810	18q22.1	TNFRSF11A	RANK	603499	
Infantile systemic hyalinosis	AR	236490	4q21	CMG2	Capillary morphogenesis gene 2	608041	Includes Juvenile Hyaline Fibromatosis (JHF, 228600) and Puretic syndrome
Mandibuloacral dysplasia type A	AR	248370	1q21.2	LMNA	Lamin A/C	150330	
Progeria, Hutchinson-Gilford type	AD	176670	1q21.2	LMNA	Lamin A/C	150330	
Mandibuloacral dysplasia type B	AR	608612	1p34	ZMPSTE24	Zinc metalloproteinase	606480	
Torg–Winchester syndrome	AR	259600	16q13	MMP2	Matrix metalloproteinase 2	120360	Includes Nodulosis-Arthropathy-Osteolysis syndrome (MIM 605156)
		277950					
Hadju–Cheney syndrome	AD	102500					
Multicentric carpal-tarsal osteolysis with and without nephropathy	AD	166300					
28. Disorganized development of skeletal components group							
Cherubism	AD	118400	4p16	SH3BP2	SH3 domain-binding protein 2	602104	
Fibrous dysplasia, polyostotic form	SP	174800	20q13	GNAS1	Guanine nucleotide-binding protein, alpha-stimulating activity subunit 1	139320	Somatic mosaicism and imprinting phenomena; includes McCune-Albright syndrome
Progressive osseous heteroplasia	AD	166350	20q13	GNAS1	Guanine nucleotide-binding protein, alpha-stimulating activity subunit 1	139320	Gene subject to imprinting
Gnathodiaphyseal dysplasia	AD	166260	11p15.1-14.3	TMEM16E	Transmembrane protein 16E	608662	

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Multiple cartilaginous exostoses 1	AD	133700	8q23-24.1	EXT1	Exostosin-1	608177	
Multiple cartilaginous exostoses 2	AD	133701	11p12-11	EXT2	Exostosin-2	608210	
Multiple cartilaginous exostoses 3	AD	600209	19p				
Osteoglophonic dysplasia	AD	166250	8p11	FGFR1	Fibroblast growth factor receptor 1	136350	See also Craniosynostosis syndromes in Group 30
Fibrodysplasia ossificans progressiva (FOP)	AD, SP	135100	2q23-24	ACVR1	Activin A (BMP type 1) receptor	102576	
Carpotarsal osteochondromatosis	AD	127820					
Cherubism with gingival fibromatosis (Ramon syndrome)	AR	266270					
Dysplasia epiphysealis hemimelica (Trevor)	SP	127800					
Enchondromatosis (Ollier)	SP	166000					PTHR1 mutations found in a few cases only
Spondyloenchondrodysplasia (SPENCD)	AR, AD?	271550					Includes SPENCD with spasticity and basal ganglia calcifications
Enchondromatosis with hemangiomata (Maffucci)	SP	166000					
Genochondromatosis	AD	137360					
Metachondromatosis	AD	156250					
Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria	SP	see 271550					
Dysspondyloenchondromatosis	SP						
Cheiro-spondyloenchondromatosis	SP						
29. Cleidocranial dysplasia group							
Cleidocranial dysplasia	AD	119600	6p21	RUNX2	Runt related transcription factor 2	600211	
CDAGS syndrome (craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, genital anomalies, skin eruption)	AR	603116	22q12-13				
Yunis-Varon dysplasia	AR	216340					
30. Craniosynostosis syndromes and other cranial ossification disorders							
Pfeiffer syndrome (FGFR1-related)	AD	101600	8p12	FGFR1	Fibroblast growth factor receptor 1	136350	All have FGFR1 P252R mutation (phenotype generally milder than FGFR2-related Pfeiffer)
Apert syndrome	AD	101200	10q26.12	FGFR2	Fibroblast growth factor receptor 2	176943	
Craniosynostosis with cutis gyrata (Beare-Stevenson)	AD	123790	10q26.12	FGFR2	Fibroblast growth factor receptor 2	176943	
Crouzon syndrome	AD	123500	10q26.12	FGFR2	Fibroblast growth factor receptor 2	176943	
Pfeiffer syndrome (FGFR2-related)	AD	101600	10q26.12	FGFR2	Fibroblast growth factor receptor 2	176943	Includes Jackson-Weiss syndrome (MIM 123150) and Antley-Bixler variants caused by FGFR2 mutations (see below)
Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome)	AD		4p16.3	FGFR3	Fibroblast growth factor receptor 3	134934	Defined by specific FGFR3 A391E mutation
Craniosynostosis Muenke type	AD	602849	4p16.3	FGFR3	Fibroblast growth factor receptor 3	134934	FGFR3 P250R mutation
Antley–Bixler syndrome	AR	201750	7q11.23	POR	Cytochrome P450 oxidoreductase	124015	Cases with FGFR2 mutations classified as Pfeiffer syndrome (MIM 207410)

(*Continued*)

TABLE I. (*Continued*)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
Craniofrontonasal syndrome	XLD	304110	Xq13.1	EFNB1	Ephrin B1	300035	
Craniosynostosis Boston type	AD	604757	5q35.2	MSX2	MSX2	123101	Heterozygous P148H mutation in a single family
Saethre–Chotzen syndrome	AD	101400	7p21.1	TWIST1	TWIST	601622	
Shprintzen–Goldberg syndrome	AD	182212					Some affected individuals reported to have FBN1 mutations (MIM 134797)
Baller–Gerold syndrome	AR	218600	8q24.3	RECQL4	RECQ Protein-like 4	603780	RECQL4 might not account for all cases of Baller-Gerold
Parietal foramina (isolated)	AD	168500	11q11.2	ALX4	Aristaless-like 4	605420	
Parietal foramina (isolated)	AD	168500	5q34-35	MSX2	Muscle segment homeobox 2	123101	
Carpenter syndrome	AR	201000					
See also Cole–Carpenter syndrome in Group 24 and CDAGS syndrome in Group 29							
31. Dysostoses with predominant craniofacial involvement							
Mandibulo-facial dysostosis (Treacher-Collins, Franceschetti-Klein)	AD	154500	5q32	TCOF1		606847	
Oral-facial-digital syndrome type I (OFD1)	XLR	311200	Xp22.3	CXORF5		300170	
Weyer acrofacial (acrodental) dysostosis	AD	193530	4p16	EVC1		604831	
Acrofacial dysostosis, Nager type	AD/AR	154400					
Frontonasal dysplasia	SP	136760					
Hemifacial microsomia	SP/AD	164210					Includes Goldenhar syndrome and Oculo-Auriculo-Vertebral spectrum; probably genetically heterogeneous
Miller syndrome (postaxial acrofacial dysostosis)	AR	263750					
See also Oral-facial-digital syndrome type IV in the Short Rib Dysplasias (Group 7)							
32. Dysostoses with predominant vertebral and costal involvement							
Currarino syndrome	AD	176450	7q36	HLXB9	Homeobox gene HB9	142994	
Spondylocostal dysostosis type 1 (SCD1)	AR	277300	19q13	Dll3	Delta-like 3	602768	
Spondylocostal dysostosis type 2 (SCD2)	AR	608681	15q26	MESP2	Mesoderm posterior (expressed in) 2	605195	
Spondylocostal dysostosis type 3 (SCD3)	AR	609713	7p22	LFNG	Lunatic fringe	602576	
Spondylocostal dysostosis, dominant type	AD						Includes previous spondylothoracic dysostosis, dominant type
Jarcho–Levin syndrome	AR						Unlinked to Dll3 or MESP2; includes previous spondylothoracic dysostosis, recessive type
Cerebro-costo-mandibular syndrome (rib gap syndrome)	AD/AR	117650					
Ischio-spinal dysostosis	SP/AR						
Klippel-Feil anomaly with laryngeal malformation	AD	148900					
See also Spondylocarpotarsal dysplasia in Group 26							

33. Patellar dysostoses							
Ischiopubic patellar dysplasia	AD	147891	17q21-q22	TBX4	T-box gene 4	601719	
Nail-patella syndrome	AD	161200	9q34.1	LMX1B	LIM homeobox transcription factor 1	602575	
Genitopatellar syndrome	AR?	606170					
Ear-patella-short stature syndrome (Meier-Gorlin)	AR	224690					
34. Brachydactylies (with or without extraskeletal manifestations)							
Brachydactyly type A1	AD	112500	2q35-36	IHH	Indian Hedgehog	600726	
Brachydactyly type A1	AD		5q31				
Brachydactyly type A2	AD	112600	4q23	BMPR1B	Bone Morphogenetic Protein Receptor, 1B	603248	
Brachydactyly type A2	AD	112600					Not linked to BMRP1B
Brachydactyly type A3	AD	112700					
Brachydactyly type B	AD	113000	9q22	ROR2	Receptor tyrosine kinase-like orphan receptor 2	602337	
Brachydactyly type B							Not linked to ROR2
Brachydactyly type C	AD, AR	113100	20q11.2	GDF5	Growth and differentiation factor 5	601146	See also ASPED (group 14) and other GDF5 disorders
Brachydactyly type D	AD	113200	2q31	HOXD13	Homeobox D13	142989	
Brachydactyly type D							Not linked to HOXD13
Brachydactyly type E	AD	113300	2q31	HOXD13	Homeobox D13	142989	
Brachydactyly type E							Not linked to HOXD13
Feingold syndrome (microcephaly-oculo-digito-esophageal-duodenal syndrome)	AD	164280	2p24.1	MYCN	nMYC oncogene	164840	
Hand-Foot-Genital	AD	140000	7p14.2	HOXA13	Homeobox A13	142959	
Keutel syndrome	AR	245150	12p13.1-12.3	MGP	Matrix Gla protein	154870	
Albright hereditary osteodystrophy (AHO)	AD	103580	20q13	GNAS1	Guanine nucleotide binding protein of adenylate cyclase—subunit	139320	See also Polyostotic fibrous dysplasia and Progressive osseous heteroplasia, Group 28
AHO-like syndrome (Brachydactyly-Mental retardation syndrome)	SP	600430	2q37				Microdeletion syndrome
Rubinstein–Taybi syndrome	AD	180849	16p13.3	CREBBP	CREB-Binding Protein	600140	
Catel–Manzke syndrome	XLR?	302380					
Christian type brachydactyly	AD	112450					
Coffin–Siris syndrome	AR	135900					
Mononen type brachydactyly	XLD?	301940					
Poland syndrome	SP	173800					
See also Group 20 for other conditions with brachydactyly							
35. Limb hypoplasia-reduction defects group							
Acheiropodia	AR	200500	7q36	LMBR1	Putative receptor protein	605522	Partial LMBR1 deletion affecting expression of Sonic Hedgehog (SHH) gene
De Lange Syndrome	AD	122470	5p13.1	NIPBL	Nipped-B-like	608667	
Fanconi anemia	AR	227650	(several)	(several)			Several complementation groups and genes
Holt–Oram syndrome	AD	142900	12q24.1	TBX5	T-box gene 5	601620	
Okihiro syndrome (Duane-Radial Ray anomaly)	AD	607323	20q13	SALL4	SAL-like 4	607343	
Roberts Syndrome	AR	268300	8p21.1	ESCO2	Homolog of Establishment of Cohesion-2	609353	

(*Continued*)

TABLE I. (*Continued*)

Name of Disorder	Inheritance	MIM No.	Locus	Gene	Protein	MIM No.	Notes
Tetra-amelia	AR	273395	17q21	WNT3	Wingless-type MMTV integration site family, member 3	165330	
Ulnar-mammary syndrome	AD	181450	12q24.1	TBX3	T-box gene 3	601621	
Ankyloblepharon-Ectodermal dysplasia-Cleft lip/palate (AEC)	AD	106260	3q27	P63 (TP63)	Tumor Protein p63	603273	
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 3 (EEC3)	AD	604292	3q27	P63 (TP63)	Tumor Protein p63	603273	
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 1 (EEC1)	AD	129900	7q11.2-12.3				
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 2 (EEC2)	AD	602077	Chr.19				
Ectrodactyly-ectodermal dysplasia-macular dystrophy syndrome (EEM)	AR	225280	16q22	CDH3	Cadherin 3	114021	
Limb-mammary syndrome (including ADULT syndrome)	AD	603273	3q27	P63 (TP63)	Tumor Protein p63	603273	
Split Hand-Foot malformation, isolated form, type 4 (SHFM4)	AD	605289	3q27	P63 (TP63)	Tumor Protein p63	603273	
Split Hand-Foot malformation, isolated form, type 1 (SHFM1)	AD	183600	7q21.3-22.1				
Split Hand-Foot Malformation, isolated form, type 2 (SHFM2)	XL	313350	Xq26				
Split Hand-Foot malformation, isolated form, type 3 (SHFM3)	AD	600095	10q24	Dactylin	Dactylin	608071	
Split Hand-Foot malformation, isolated form, type 5 (SHFM5)	AD	606708	2q31				
Split Hand-Foot malformation with tibial hypoplasia	AD	119100					
Adams–Oliver syndrome	AD	100300					
Al-Awadi Raas-Rothschild limb-pelvis hypoplasia-aplasia	AR	276820					
Femoral hypoplasia-Unusual facies syndrome	SP/AD?	134780					Syndromic status uncertain
Femur–Fibula–Ulna syndrome	SP?	228200					
Fuhrmann syndrome	AR	228930					
Hanhart syndrome (Hypoglossia-hypodactylia)	AD	103300					
Scapulo-iliac dysplasia (Kosenow)	AD	169550					
Thrombocytopenia-Absent Radius (TAR)	AR?/AD?	274000					
See also CHILD in Group 20							
36. Polydactyly-Syndactyly-Triphalangism group							
Preaxial Polydactyly type 1 (PPD1)	AD	174400	7q36	SHH	Sonic Hedgehog	600725	Regulatory mutation
Preaxial Polydactyly type 1 (PPD1)	AD	174400					Some instances not linked to SHH
Preaxial Polydactyly type 2 (PPD2)/Triphalangeal Thumb (TPT)	AD	174500	7q36	SHH	Sonic Hedgehog	600725	Regulatory mutation
Preaxial Polydactyly type 2 (PPD2)/Triphalangeal Thumb (TPT)	AD	174500					Some instances not linked to SHH
Preaxial Polydactyly type 3(PPD3)	AD	174600					
Preaxial Polydactyly type 4 (PPD4)	AD	174700	7p13	GLI3	Gli-Kruppel Family Member 3	165240	
Greig Cephalopolysyndactyly syndrome	AD	175700	7p13	GLI3	Gli-Kruppel Family Member 3	165240	
Pallister–Hall syndrome	AD	146510	7p13	GLI3	Gli-Kruppel Family Member 3	165240	

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Fibulin1—associated complex synpolydactyly	AD	608180	22q13.3	FBLN1	Fibulin 1	135820	
Synpolydactyly	AD	186000	2q31	HOXD13	Homeobox D13	142989	
Syndactyly type 3	AD	186100	6q22-24	CX43	Connexin 43	121014	
Townes–Brocks syndrome (Renal-Ear-Anal-Radial syndrome)	AD	107480	16q12.1	SALL1	SAL-like 1	602218	
Lacrimo-Auriculo-Dento-Digital syndrome (LADD)	AD	149730	10q26.12	FGFR2	Fibroblast growth factor receptor 2	176943	
			4p16.3	FGFR3	Fibroblast growth factor receptor 3	134934	
			5p13-p12	FGF10	Fibroblast growth factor 10	602115	
Acrocallosal syndrome	AR	200990	7p13				
Acro-pectoral syndrome	AD	605967	7q36				
Acro-pectoro-vertebral dysplasia (F-syndrome)	AD	102510	2q36				
Mirror-image polydactyly of hands and feet (Laurin–Sandrow syndrome)	AD	135750	14q13				
Mirror-image polydactyly of feet with tibial hypoplasia	AD	188770					
Syndactyly type 1	AD	185900	2q34-36				
Postaxial Polydactyly			Several loci				Heterogeneous
37. Defects in joint formation and synostoses							
Multiple synostoses syndrome type 1	AD	186500	17q22	NOG	Noggin	602991	Includessymphalangism-brachydactyly-deafness syndrome
Multiple synostoses syndrome type 2	AD	186500	20q11.2	GDF5	Growth and Differentiation Factor 5	601146	
Proximal symphalangism type 1	AD	185800	17q22	NOG	Noggin	602991	
Proximal symphalangism type 2	AD	185800	20q11.2	GDF5	Growth and Differentiation Factor 5	601146	
Radio-ulnar synostosis with amegakaryocytic thrombocytopenia	AD	605432	7p15-14.2	HOXA11	Homeobox A11	142958	
See also Spondylo-Carpal-Tarsal dysplasia (Group 6); Mesomelic Dysplasia with Acral Synostoses (Group 16); Antley Bixler syndrome (Group 30)							

number of disorders that are listed in MIM but have been found not to meet inclusion criteria, in most instances because of too few observations or because of the lack of features allowing clear diagnostic distinction from other disorders. It is likely that additional observations or molecular elucidation will allow for the inclusion of many of these disorders in the future, either as distinct entities or as "variants" of already existing ones. In this sense, the Nosology illustrates the many things we do not yet know.

The organization of disorders into Groups has been changed significantly compared to the 2001 version [Hall, 2002]. More groups based on a common affected molecule or biochemical pathway have been created (Groups 1–6). Several groups are based on the anatomical localization of radiographic changes (Groups 7–16). Groups 17–19 are defined by macroscopic criteria and clinical features (bent bones, slender bones, presence of multiple dislocations). Groups 20–25 and 27 take into account features of mineralization (increased or reduced bone density, disturbed mineralization stippling, osteolysis). Group 26 encompasses the large group of lysosomal disorders with skeletal involvement. Group 28 comprises disorders with so-called abnormal development of skeletal components such as exostoses, ecnhondromas, and ectopic calcification. This group is quite heterogeneous and may need to be revised in the future with the help of newer molecular data. Finally, Groups 29–37 are dedicated to the dysostoses (with Group 29 including cleidocranial dysplasia as a well-known example of transition between dysplasia and dysostosis) that follow again anatomical criteria (cranium, face, axial skeleton, extremities) with additional criteria reflecting principles of embryonal development such as limb reduction or hypoplasia (proximal-distal growth) versus terminal differentiation and patterning of the digits or joint formation. Additionally we have converted all Roman numerals to Arabic numbering to make electronic searches more straight forward.

Criticism to the previous versions of the Nosology has focussed on its "hybrid" nature, in the sense that it does not stick to a systematic approach, be it clinical or molecular. It is true that the Nosology is not necessarily aimed at being a diagnostic tool; other papers can be more useful in this respect [Unger, 2002; Offiah and Hall, 2003]. On a similar line, other papers have focused on the molecular aspects of genetic disorders of bone [Hermanns and Lee, 2001; Superti-Furga et al., 2001; Kornak and Mundlos, 2003]. Thus, the Nosology should coexist with other classifications based on the clinical and radiographic approach to diagnosis or based on the affected molecular systems and pathways, and it is hoped that electronic means will facilitate transition and interactions between the various classification criteria that can be applied. Efforts are in place to establish a web-based system enabling databases searches for molecular defects, pathways, and clinical features.

In spite of these limitations, the Nosology can offer a rapid help and orientation in this complex field. For the clinician who is struggling for a diagnosis, a simple listing of disorders grouped by cardinal features can help in indicating the way of further enquiries and consultation of appropriate sources. The boundaries between skeletal dysplasias and dysostoses, metabolic and molecular disorders, and multiple congenital anomalies syndromes is becoming progressively less sharp, and the diagnostic process requires knowledge that crosses the boundaries between these subspecialty areas. For the expert, the Nosology offers a quick reminder of the many differential diagnoses for one given disorder. In some instances, the Nosology as the list of currently recognized disorders will constitute the standard against which a possible "new" disorder should be compared. And last but not least, the Nosology offers a catalogue of genes involved in skeletal development and homeostasis and should be of interest and of inspiration to all those who are working in skeletal biology and medicine.

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