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Progress in Medical Genetics: Map–Based Gene Discovery and the Molecular Pathology of Skeletal Dysplasias

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INTRODUCTION

We at Johns Hopkins first met Jurgen Spranger on May 20, 1968 when he came to Baltimore to attend the first of five annual conferences on the Clinical Delineation of Birth Defects. Two days of that 5 1/2 day conference were devoted to a discussion of skeletal dysplasias. The proceedings were published as a rather weighty book [Bergsma et al., 1969]. In that conference, papers were presented by invited participants morning and afternoon, and at the noon hour a considerable number of highly instructive patients were presented in person for discussion by the group. For example, the late John Strudwick, who represented the prototype case of Strudwick type spondyloepimetaphyseal dysplasia congenita, or dappled metaphysis syndrome, was one of the patients presented. The group in attendance included most of the leading orthopedists and radiologists as well as pediatric endocrinologists and medical geneticists who were students of skeletal dysplasias. In addition to Spranger, Lamy, Langer, Silverman, Gorlin, Rimoin, Hall, Taybi, Dent, Leroy, Winchester, and others presented papers. There was a charisma associated with that first conference, and the four more held at Johns Hopkins, that sparked a new age in clinical genetics. James German, who had been chief of the genetics division in the department of pediatrics at Cornell Medical College and the New York Hospital, commented that if he had known that clinical genetics could be so much fun (presumably meaning intellectual excitement) he would not have left Cornell to go to the New York Blood Center.

All the topics (and not the least the skeletal dysplasias) that were discussed in those jam–packed days of the five annual conferences (1968–1972) have shown great progress since that time. Nosology and understanding of the nature of the basic defect have been main points of focus, but management in all of its dimensions has also been important to all of us involved in the study of these conditions, and much remains to be learned about the natural history and clinical course, particularly of the rarer disorders.

MAPPING SKELETAL DYSPLASIAS

Both nosology and understanding of the basic defect—and these are, of course, related matters—have been greatly aided by the processes of gene mapping and map-based gene discovery. Main strategies have been positional cloning (i.e., "walking in on" the previously unknown gene from markers that flank the region where the phenotype maps) and the positional candidate gene approach [Collins, 1995] (i.e., the spotting of genes coding for particular enzymes or other proteins that map to the same region as the clinical phenotype and could plausibly be the site of the mutation). With both approaches, demonstration of specific mutations in the gene in question clinches the fact that the basic defect resides therein. Here we will review the mapping of skeletal dysplasias and the elucidation of the molecular pathology of these disorders that has come out of the mapping.

The accompanying tables (Tables IA and IB)[1] present a list of skeletal dysplasias that have been mapped to date. In the definition of skeletal dysplasia, we have exercised some license. In addition to the disorders in the International Classification of Osteochondrodysplasias [International Working Group, 1992], we have included several forms of the Ehlers–Danlos syndrome due to defects in collagens. We have also included hand malformations, both syndromic and nonsyndromic, and we have included the craniosynostoses and craniofacial dysostoses. We did not include Gorlin syndrome, neurofibromatosis type I, or fragile X syndrome, although these disorders sometimes show striking skeletal and connective tissue involvement. We have also not included the various growth hormone deficiency states

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

[1]Up–to–date information on each of the disorders discussed in the text and in Tables IA and IB is available, together with bibliographic references, in OMIM. The six–digit MIM number indicates the appropriate entry in OMIM in each case. OMIM is accessed through the following internet address: http://www3.ncbi.nlm.nih.gov/omim/.

TABLE IA. The Mapping of Skeletal Dysplasias: Listing of Loci of One or More Skeletal Dysplasias by Chromosomal Location*

Location	Symbol	Title	MIM#	Disorder	Mouse
1p36.3	MTHFR	Methylenetetrahydrofolate reductase	236250	Homocystinuria due to MTHFR deficiency (3)	
1p36.1-p34	ALPL, HOPS	Alkaline phosphatase, liver/bone/kidney	171760	Hypophosphatasia, infantile, 241500 (3); ?Hypophosphatasia, adult, 146300 (1)	4(Akp2)
1p34	FUCA1	Fucosidase, alpha-L-1, tissue	230000	Fucosidosis (3)	4(Fuca)
1p32	EDM2	Epiphyseal dysplasia, multiple 2	600204	Epiphyseal dysplasia, multiple 2 (2)	
1p21-p13	CSF1, MCSF	Colony-stimulating factor-1 (macrophage)	120420	?Osteopetrosis, 259700 (1)	3(Csfm)
1p21	PKND	Pyknodysostosis (pycnodysostosis)	265800	Pycnodysostosis (2)	
2q31	COL3A1	Collagen, type III, alpha-1 polypeptide	120180	Ehlers-Danlos syndrome, type IV, 130050 (3); Aneurysm, familial, 100070 (3); Fibromuscular dysplasia of arteries, 135580 (3); Ehlers-Danlos syndrome, type III (3)	1(Col3a1)
2q31	SPD	Syndactyly type II (synpolydactyly)	186000	Syndactyly, type II (2)	
3p22-p21.1	PTHR	Parathyroid hormone receptor	168468	Metaphyseal chondrodysplasia, Murk Jansen type, 156400 (3)	
3p21.33	GLB1	Galactosidase, beta-1	230500	GM1-gangliosidosis (3); Mucopolysaccharidosis IVB (3)	9(Bgl)
3p21.1-p14.1	LRS1, LAR1	Larsen syndrome 1 (autosomal dominant)	150250	Larsen syndrome, autosomal dominant (2)	
3p13-p12	BBS3	Bardet-Biedl syndrome 3	600151	Bardet-Biedl syndrome 3 (2)	
3q21-q24	HHC1, FHH, PCAR1	Hypocalciuric hypercalcemia-1 (parathyroid Ca(2+)-sensing receptor)	145980	Hypercalcemia, hypocalciuric, type I (3); Neonatal hyperparathyroidism, 239200 (3); Hypocalcemia, autosomal dominant (3)	
4p16.3	FGFR3, ACH	Fibroblast growth factor receptor-3	134934	Achondroplasia, 100800 (3); Hypochondroplasia, 146000 (3); Thanatophoric dwarfism, 187600 (3)	5(Fgfr3)
4p16.3	IDUA, IDA	Iduronidase, alpha-L-	252800	Mucopolysaccharidosis Ih (3); Mucopolysaccharidosis Is (3); Mucopolysaccharidosis Ih/s (3)	5(Idua)
4p16	CRSA, CRS3	Craniosynostosis, Adelaide type	600593	Craniosynostosis, Adelaide type (2)	
4p16	EVC	Ellis-van Creveld syndrome	225500	Ellis-van Creveld syndrome (2)	
4p16-p14	CDPR	Chondrodysplasia punctata, rhizomelic	215100	?Chondrodysplasia punctata, rhizomelic (2)	
4q21-q23	GNPTA	UDP-N-acetylglucosamine-lysosomal-enzyme N-acetylglucosamine phosphotransferase	252500	Mucolipidosis II (1); Mucolipidosis III (1)	
4q32-q33	AGA	Aspartylglucosaminidase	208400	Aspartylglucosaminura (3)	
5q11-q13	ARSB	Arylsulfatase B	253200	Maroteaux-Lamy syndrome, several forms (3)	13(As1)
5q11.2	KFS	Klippel-Feil syndrome	214300	?Klippel-Feil syndrome (2)	
5q23-q31	FBN2, CCA	Fibrillin-2	121050	Contractural arachnodactyly, congenital (3)	18(Fbn2)
5q31-q34	DTD, DTDST, D5S1708	Diastrophic dysplasia sulfate transporter	222600	Diastrophic dysplasia (3); Atelosteogenesis II, 256050 (3); Achondrogenesis Ib, 600972 (3)	
5q32-q33.1	TCOF1, MFD1	Treacher Collins-Franceschetti syndrome-1	154500	Treacher Collins mandibulofacial dysostosis (2)	
5q34-q35	MSX2, CRS2, HOX8	msh (Drosophila) homeo box homolog 2	123101	Craniosynostosis, type 2 (3)	
6p21.3	COL11A2	Collagen XI, alpha-2 polypeptide	120290	Stickler syndrome, type II, 184840 (3); OSMED syndrome, 215150 (3)	17(Col11a2)
6p21	CCD	Cleidocranial dysplasia	119600	Cleidocranial dysplasia (2)	
6q21-q22.3	COL10A1	Collagen, type X, alpha-1 polypeptide	120110	Metaphyseal chondrodysplasia, Schmid type (3)	10(Col10a1)

(*continued*)

TABLE IA. (*continued*)

Location	Symbol	Title	MIM#	Disorder	Mouse
7p21.3-p21.2	CRS, CSO	Craniosynostosis, type I	123100	Craniosynostosis, type 1 (2)	
7p21	ACS3, SCS	Acrocephalosyndactyly-3 (Saethre-Chotzen syndrome)	101400	Saethre-Chotzen syndrome (2)	
7p13	GL13	GLI-Kruppel family member GL13 (oncogene GL13)	165240	Greig cephalopolysyndactyly syndrome, 175700 (3)	13(Xt)
7p	GHS	Goldenhar syndrome	141400	?Goldenhar syndrome (2)	
7q21.11	GUSB	Glucuronidase, beta-	253200	Mucopolysaccharidosis VII (3)	5(Gus)
7q21.2-q21.3	SHFM1, SHFD1, SHSF1	Split hand/foot malformation, type 1	183600	Split-hand/split-foot malformation, type 1 (2)	
7q22.1	COL1A2	Collagen, type I, alpha-2 polypeptide	120160	Osteogenesis imperfecta, 4 clinical forms, 166200, 166210, 259420, 166220 (3); Ehlers-Danlos syndrome, type VIIA2, 130060 (3)	6(Cola2)
7q36	HPE3, HLP3	Holoprosencephaly-3	142945	Holoprosencephaly, type 3 (2)	
7q36	TPT1	Triphalangeal thumb-polysyndactyly syndrome	190605	Triphalangeal thumb-polysyndactyly syndrome (2)	
8p11.2-p11.1	FGFR1, FLT2	Fibroblast growth factor receptor-1 (fms-related tyrosine kinase-2)	136350	Pfeiffer syndrome, 101600 (3)	
8q	CCAL1	Chondrocalcinosis 1 (calcium pyrophosphate-deposition disease, early onset osteoarthritis)	118600	Chondrocalcinosis with early onset osteoarthritis (2)	
8q22	CA2	Carbonic anhydrase II	259730	Renal tubular acidosis-osteopetrosis syndrome (3)	3(Car2)
8q24.11-q24.13	EXT1	Exostoses (multiple) 1	133700	Exostoses, multiple, type 1 (2)	
8q24.11-q24.13	LGCR, LGS, TRPS2	Langer-Giedion syndrome chromosome region	150230	Langer-Giedion syndrome (2)	
8q24.12	TRPS1	Trichorhinophalangeal syndrome, type I	190350	Trichorhinophalangeal syndrome, type I (2)	
9p13	CHH	Cartilage-hair hypoplasia	250250	Cartilage-hair hypoplasia (2)	
9q32	AFDN	Acrofacial dysostosis, Nager type	154400	?Acrofacial dysostosis, Nager type (2)	
9q34.1	NPS1	Nail-patella syndrome	161200	Nail-patella syndrome (2)	
9q34.2-q34.3	EDS2	Ehlers-Danlos syndrome, type II	130010	Ehlers-Danlos syndrome, type II (2)	
9q34.2-q34.3	COL5A1	Collagen V, alpha-1 polypeptide	120215	?Ehlers-Danlos syndrome, type II, one form, 130010 (2)	2(COL5a1)
10q26	FGFR2, BEK, CFD1, JWS	Fibroblast growth factor receptor-2 (bacteria-expressed kinase)	176943	Crouzon craniofacial dysostosis, 123500 (3); Jackson-Weiss syndrome, 123150 (3); Apert syndrome, 101200 (3); Pfeiffer syndrome, 101600 (3)	7(Fgfr2)
11p12-p11	EXT2	Exostoses (multiple) 2	133701	Exostoses, multiple, type 2 (2)	
11q13	BBS1	Bardet-Biedl syndrome 1	209901	Bardet-Biedl syndrome 1 (2)	
12p13.3-p11.2	ACLS	Acrocallosal syndrome	200990	?Acrocallosal syndrome (2)	
12q	ORW2, HHT2	Osler-Rendu-Weber syndrome 2	600376	Hereditary hemorrhagic telangiectasia, type II (2)	
12q13.11-q13.2	COL2A1	Collagen, type II, alpha-1 polypeptide	120140	Stickler syndrome, type 1 (3); SED congenita (3); Kniest dysplasia (3); Achondrogenesis-hypochondrogenesis, type II (3); Osteoarthrosis, precocious (3); Wagner syndrome, type II (3); SMED Strudwick type (3)	
12q14	GNS, G6S	N-acetylglucosamine-6-sulfatase	252940	Sanfilippo syndrome, type D (1)	
12q21.3-q22	HOS	Holt-oram syndrome	142900	Holt-Oram syndrome (2)	
14q11.1-q13	HPE4	Holoprosencephaly-4, semilobar	142946	?Holoprosencephaly-4 (2)	
Chr.14	MPS3C	Mucopolysaccharidosis, type IIIC	252930	?Sanfilippo syndrome, type C (2)	
15q21.1	FBN1, MFS1	Fibrillin-1	134797	Marfan syndrome, 154700 (3)	2(Fbn1)

15q22.3-q23	BBS4	Bardet-Biedl syndrome 4	600374	Bardet-Biedl syndrome 4 (2)	
16p13.3	CREBBP, CBP, RSTS	CREB binding protein	600140	Rubenstein-Taybi syndrome, 180849 (3)	
16q21	BBS2	Bardet-Biedl syndrome 2	209900	Bardet-Biedl syndrome 2 (2)	
16q24.3	GALNS, MPS4A	Galactosamine (N-acetyl)-6-sulfate sulfatase	253000	Mucopolysaccharidosis IVA (3)	
17q21	NAGLU	N-acetylglucosaminidase, alpha-	252920	Sanfilippo syndrome, type B (3)	
17q21-q22	SYM1	Symphalangism 1 (proximal)	185800	Symphalangism, proximal (2)	
17q21.31-q22.05	COL1A1	Collagen I, alpha-1 polypeptide	120150	Osteogenesis imperfecta, 4 clinical forms, 166200, 166210, 259420, 166220 (3); Ehlers-Danlos syndrome, type VIIA1, 130060 (3); Osteoporosis, idiopathic, 166710 (3)	11(Cola1)
17q24.3-q25.1	CMD1, SOX9, SRA1	Campomelic dysplasia-1 (sex reversal, autosomal, 1)	211970	Campomelic dysplasia with autosomal sex reversal (3)	11(Ts, Sox9)
17q25	RSS	Russell-Silver syndrome	180860	Russell-Silver syndrome (2)	
18pter-q11	HPE1	Holoprosencephaly-1, alobar	236100	?Holoprosencephaly-1 (2)	
18q21.1-q22	FEO	Familial expansile osteolysis	174810	Familial expansile osteolysis (2)	
19p13.1	COMP, EDM1, MED, PSACH	Cartilage oligomeric matrix protein	600310	Pseudoachondroplasia, 177170 (3); Epiphyseal dysplasia, multiple-1, 132400 (3)	
19p	EXT3	Exostoses (multiple) 3	600209	Exostoses, multiple, type 3 (2)	
19cen-q12	MANB	Mannosidase, alpha B, lysosomal	248500	Mannosidosis, alpha- (1)	
20p12	BMP2, BMP2A	Bone morphogenetic protein-2	112261	?Fibrodysplasia ossificans progressiva (1)	2(Bmp2a)
20q13.11	ADA	Adenosine deaminase	102700	Severe combined immunodeficiency due to ADA deficiency (3); Hemolytic anemia due to ADA excess (1)	2(Ada)
20q13.2	GNAS1, GNAS, GPSA	Guanine nucleotide-binding protein (G protein), alpha-stimulating activity polypeptide-1	139320	Pseudohypoparathyroidism, type Ia, 103580 (3); McCune-Albright polyostotic fibrous dysplasia, 174800 (3); Somatotrophinoma (3); Pituitary ACTH secreting adenoma (3)	2(Gnas)
21q22.3	CBS	Cystathionine beta-synthase	236200	Homocystinuria, B6-responsive and nonresponsive types (3)	17(Cbs)
Xpter-p22.2	CFND	Craniofrontonasal dysplasia	304110	?Craniofrontonasal dysplasia (2)	
Xp22.3	ARSE, CDPX1, CDPXR	Arylsulfatase E	302950	Chondrodysplasia punctata, X-linked recessive, 302940 (3)	
Xp22.2-p22.1	HYP, HPDR1	Hypophosphatemia, vitamin D resistant rickets	307800	Hypophosphatemia, hereditary (3)	X(Hyp)
Xp22.2-p22.1	SEDL, SEDT	Spondyloepiphyseal dysplasia, late	313400	Spondyloepiphyseal dysplasia tarda (2)	
Xq26	SHFM2, SHFD2	Split hand/foot malformation, type (ectrodactyly) 2	313350	Split hand/foot malformation, type 2 (2)	
Xq28	CDPX2, CPXD, CPX	Chondrodysplasia, punctata-2, X-linked dominant (Happle syndrome)	302960	Chondrodysplasia punctata, X-linked dominant (2)	X(Bpa)
Xq28	IDS, MPS2, SIDS	Iduronate 2-sulfatase (Hunter syndrome)	309900	Mucopolysaccharidosis II (3)	X(Ids)
Xq28	OPD1	Otopalatodigital syndrome, type I	311300	Otopalatodigital syndrome, type I (2)	

*Information on the specific disorders, with bibliographic references, is available on line in OMIM in entries identified by the six-digit MIM number.

TABLE IB. The Mapping of Skeletal Dysplasias: Alphabetic Listing of the Mapped Skeletal Dysplasias*

Disorder	Location	Symbol	Title	MIM#
Achondrogenesis Ib, 600972 (3)	5q31-q34	DTD, DTDST, D5S1708	Diastrophic dysplasia sulfate transporter	222600
Achondrogenesis-hypochondrogenesis, type II (3)	12q13.11-q13.2	COL2A1	Collagen, type II, alpha-1 polypeptide	120140
Achondroplasia, 100800 (3)	4p16.3	FGFR3, ACH	Fibroblast growth factor receptor-3	134934
?Acrocallosal syndrome (2)	12p13.3-p11.2	ACLS	Acrocallosal syndrome	200990
?Acrofacial dysostosis, Nager type (2)	9q32	AFDN	Acrofacial dysostosis, Nager type	154400
Aneurysm, familial, 100070 (3)	2q31	COL3A1	Collagen, type III, alpha-1 polypeptide	120180
Apert syndrome, 101200 (3)	10q26	FGFR2, BEK, CFD1, JWS	Fibroblast growth factor receptor-2 (bacteria-expressed kinase)	176943
Aspartylglucosaminuria (3)	4q32-q33	AGA	Aspartylglucosaminidase	208400
Atelosteogenesis II, 256050 (3)	5q31-q34	DTD, DTDST, D5S1708	Diastrophic dysplasia sulfate transporter	222600
Bardet-Biedl syndrome 1 (2)	11q13	BBS1	Bardet-Biedl syndrome 1	209901
Bardet-Biedl syndrome 2 (2)	16q21	BBS2	Bardet-Biedl syndrome 2	209900
Bardet-Biedl syndrome 3 (2)	3p13-p12	BBS3	Bardet-Biedl syndrome 3	600151
Bardet-Biedl syndrome 4 (2)	15q22.3-q23	BBS4	Bardet-Biedl syndrome 4	600374
Campomelic dysplasia with autosomal sex sex reversal (3)	17q24.3-q25.1	CMD1, SOX9, SRA1	Campomelic dysplasia-1 (sex reversal, autosomal, 1)	211970
Cartilage-hair hypoplasia (2)	9p13	CHH	Cartilage-hair hypoplasia	250250
Chondrocalcinosis with early onset osteoarthritis (2) osteoarthritis (2)	8q	CCAL1	Chondrocalcinosis 1 (calcium pyrophosphate-deposition disease, early onset osteoarthritis)	118600
?Chondrodysplasia punctata, rhizomelic (2)	4p16-p14	CDPR	Chondrodysplasia punctata, rhizomelic	215100
Chondrodysplasia punctata, X-linked dominant (2)	Xq28	CDPX2, CPXD, CPX	Chondrodysplasia punctata-2, X-linked dominant (Happle syndrome)	302960
Chondrodysplasia punctata, X-linked recessive, 302940 (3)	Xp22.3	ARSE, CDPX1, CDPXR	Arylsulfatase E	302950
Cleidocranial dysplasia (2)	6p21	CCD	Cleidocranial dysplasia	119600
Contractural arachnodactyly, congenital (3)	5q23-q31	FBN2, CCA	Fibrillin-2	121050
?Craniofrontonasal dysplasia (2)	Xpter-p22.2	CFND	Craniofrontonasal dysplasia	304110
Craniosynostosis, Adelaide type (2)	4p16	CRSA, CRS3	Craniosynostosis, Adelaide type	600593
Craniosynostosis, type 1 (2)	7p21.3-p21.2	CRS, CSO	Craniosynostosis, type I	123100
Craniosynostosis, type 2 (3)	5q34-q35	MSX2, CRS2, HOX8	msh (Drosophila) homeo box homolog 2	123101
Crouzon craniofacial dysostosis, 123500 (3)	10q26	FGFR2, BEK, CFD1, JWS	Fibroblast growth factor receptor-2 (bacteria-expressed kinase)	176943
Diastrophic dysplasia (3)	5q31-q34	DTD, DTDST, D5S1708	Diastrophic dysplasia sulfate transporter	222600
Ehlers-Danlos syndrome, type II (2)	9q34.2-q34.3	EDS2	Ehlers-Danlos syndrome, type II	130010
?Ehlers-Danlos syndrome, type II, one form, 1300010 (2)	9q34.2-q34.3	COL5A1	Collagen V, alpha-1 polypeptide	120215
Ehlers-Danlos syndrome, type III (3)	2q31	COL3A1	Collagen, type III, alpha-1 polypeptide	120180
Ehlers-Danlos syndrome, type IV, 130050 (3)	2q31	COL3A1	Collagen, type III, alpha-1 polypeptide	120180
Ehlers-Danlos syndrome, type VIIA1, 130060 (3)	17q21.31-q22.05	COL1A1	Collagen, alpha-1 polypeptide	120150
Ehlers-Danlos syndrome, type VIIA2, 130060 (3)	7q22.1	COL1A2	Collagen, type I, alpha-2 polypeptide	120160
Ellis-van Creveld syndrome (2)	4p16	EVC	Ellis-van Creveld syndrome	225500
Epiphyseal dysplasia, multiple 2 (2)	1p32	EDM2	Epiphyseal dysplasia, multiple 2	600204
Epiphyseal dysplasia, multiple 1, 132400 (3)	19p13.1	COMP, EDM1, MED, PSACH	Cartilage oligomeric matrix protein	600310
Exostoses, multiple, type 1 (2)	8q24.11-q24.13	EXT1	Exostoses (multiple) 1	133700
Exostoses, multiple, type 2 (2)	11p12-p11	EXT2	Exostoses (multiple) 2	133701
Exostoses, multiple, type 3 (2)	19p	EXT3	Exostoses (multiple) 3	600209
Familial expansile osteolysis (2)	18q21.1-q22	FEO	Familial expansile osteolysis	174810
?Fibrodysplasia ossificans progressiva (1)	20p12	BMP2, BMP2A	Bone morphogenetic protein-2	112261

Fibromuscular dysplasia of arteries, 135580 (3)	2q31	COL3A1	Collagen, type III, alpha-1 polypeptide	120180
Fucosidosis (3)	1p34	FUCA1	Fucosidase, alpha-L-1, tissue	230000
GM1-gangliosidosis (3)	3p21.33	GLB1	Galactosidase, beta-1	230500
?Goldenhar syndrome (2)	7p	GHS	Goldenhar syndrome	141400
Greig cephalopolysyndactyly syndrome, 175700 (3)	7p13	GLI3	GLI-Kruppel family member GLI3 (oncogene GLI3)	165240
Hemolytic anemia due to ADA excess (1)	20q13.11	ADA	Adenosine deaminase	102700
Hereditary hemorrhagic telangiectasia, type II (2)	12q	ORW2, HHT2	Osler-Rendu-Weber syndrome 2	600376
Holoprosencephaly, type 3 (2)	7q36	HPE3, HLP3	Holoprosencephaly-3	142945
?Holoprosencephaly-1 (2)	18pter-q11	HPE1	Holoprosencephaly-1, alobar, 236100	
?Holoprosencephaly-4 (2)	14q11.1-q13	HPE4	Holoprosencephaly-4, semilobar	142946
Holt-Oram syndrome (2)	12q21.3-q22	HOS	Holt-Oram syndrome	142900
Homocystinuria, B6-responsive and nonresponsive types (3)	21q22.3	CBS	Cystathionine beta-synthase	236200
Homocystinura due to MTHFR deficiency (3)	1p36.3	MTHFR	Methylenetetrahydrofolate reductase	236250
Hypercalcemia, hypocalciuric, type I (3)	3q21-q24	HHC1, FHH, PCAR1	Hypocalciuric hypercalcemia-1 (parathyroid Ca(2+)-sensing receptor)	145980
Hypocalcemia, autosomal dominant (3)	3q21-q24	HHC1, FHH, PCAR1	Hypocalciuric hypercalcemia-1 (parathyroid Ca(2+)-sensing receptor)	145980
Hypochondrodysplasia, 14600 (3)	4p16.3	FGFR3, ACH	Fibroblast growth factor receptor-3	134934
?Hypophosphatasia, adult, 146300 (1)	1p36.1-p34	ALPL, HOPS	Alkaline phosphatase, liver/bone/kidney	171760
Hypophosphatasia, infantile, 241500 (3)	1p36.1-p34	ALPL, HOPS	Alkaline phosphatase, liver/bone/kidney	171760
Hypophosphatemia, hereditary (3)	Xp22.2-p22.1	HYP, HPDR1	Hypophosphatemia, vitamin D resistant rickets	307800
Jackson-Weiss syndrome, 123150 (3)	10q26	FGFR2, BEK, CFD1, JWS	Fibroblast growth factor receptor-2 (bacteria-expressed kinase)	176943
?Klippel-Feil syndrome (2)	5q11.2	KFS	Klippel-Feil syndrome	214300
Kniest dysplasia (3)	12q13.11-q13.2	COL2A1	Collagen, type II, alpha-1 polypeptide	120140
Langer-Giedion syndrome (2)	8q24.11-q24.13	LGCR, LGS, TRPS2	Langer-Giedion syndrome chromosome region	150230
Larsen syndrome, autosomal dominant (2)	3p21.1-p14.1	LRS1, LAR1	Larsen syndrome 1 (autosomal dominant)	150250
Mannosidosis, alpha- (1)	19cen-q12	MANB	Mannosidase, alpha B, lysosomal	248500
Marfan syndrome, 154700 (3)	15q21.1	FBN1, MFS1	Fibrillin-1	134797
Maroteaux-Lamy syndrome, several forms (3)	5q11-q13	ARSB	Arylsulfatase B	253200
McCune-Albright polyostotic fibrous dysplasia, 174800 (3)	20q13.2	GNAS1, GNAS, GPSA	Guanine nucletide-binding protein (G protein), alpha-stimulating activity polypeptide-1	139320
Metaphyseal chondrodysplasia, Murk Jansen type, 156400 (3)	3p22-p21.1	PTHR	Parathyroid hormone receptor	168468
Metaphyseal chondrodysplasia, Schmid type (3)	6q21-q22.3	COL10A1	Collagen, type X, alpha-1 polypeptide	120110
Mucolipidosis II (1)	4q21-q23	GNPTA	UDP-N-acetylglucosamine-lysosomal-enzyme N-acetylglucosamine phosphotransferase	252500
Mucolipidosis III (1)	4q21-q23	GNPTA	UDP-N-acetylglucosamine-lysosomal-enzyme N-acetylglucosamine phosphotransferase	252500
Mucopolysaccharidosis Ih (3)	4p16.3	IDUA, IDA	Iduronidase, alpha-L-	252800
Mucopolysaccharidosis Ih/s (3)	4p16.3	IDUA, IDA	Iduronidase, alpha-L-	252800
Mucopolysaccharidosis II (3)	Xq28	IDS, MPS2, SIDS	Iduronate 2-sulfatase (Hunter syndrome)	309900
Mucopolysaccharidosis IVA (3)	16q24.3	GALNS, MPS4A	Galactosamine (N-acetyl)-6-sulfate sulfatase	253000
Mucopolysaccharidosis IVB (3)	3p21.33	GLB1	Galactosidase, beta-1	230500
Mucopolysaccharidosis VII (3)	7q21.11	GUSB	Glucuronidase, beta-	253220
Nail-patella syndrome (2)	9q34.1	NPS1	Nail-patella syndrome	161200
Neonatal hyperparathyroidism, 239200 (3)	3q21-q24	HHC1, FHH, PCAR1	Hypocalciuric hypercalcemia-1 (parathyroid Ca(2+)-sensing receptor)	145980
OSMED syndrome, 215150 (3)	6p21.3	COL11A2	Collagen XI, alpha-2 polypeptide	120290
Osteoarthrosis, precocious (3)	12q13.11-q13.2	COL2A1	Collagen, type II, alpha-1 polypeptide	120140

(*continued*)

TABLE IB. (*continued*)

Disorder	Location	Symbol	Title	MIM#
Osteogenesis imperfecta, 4 clinical forms, 166200, 166210, 259420, 166220 (3)	17q21.31-q22.05	COL1A1	Collagen I, alpha-1 polypeptide	120150
Osteogenesis imperfecta, 4 clinical forms, 166200, 166210, 259420, 166220 (3)	7q22.1	COL1A2	Collagen, type I, alpha-2 polypeptide	120160
?Osteopetrosis, 259700 (1)	1p21-p13	CSF1, MCSF	Colony-stimulating factor-1 (macrophage)	120420
Osteoporosis, idiopathic, 166710 (3)	17q21.31-q22.05	COL1A1	Collagen I, alpha-1 polypeptide	120150
Otopalatodigital syndrome, type I (2)	Xq28	OPD1	Otopalatodigital syndrome, type I	311300
Pfeiffer syndrome, 101600 (3)	10q26	FGFR2, BEK, CFD1, JWS	Fibroblast growth factor receptor-2 (bacteria-expressed kinase)	176943
Pfeiffer syndrome, 101600 (3)	8p11.2-p11.1	FGFR1, FLT2	Fibroblast growth factor receptor-1 (fms-related tyrosine kinase-2)	136350
Pituitary ACTH secreting adenoma (3)	20q13.2	GNAS1, GNAS, GPSA	Guanine nucleotide-binding protein (G protein), alpha-stimulating activity polypeptide-1	139320
Pseudoachondroplasia, 177170 (3)	19p13.1	COMP, EDM1, MED, PSACH	Cartilage oligomeric matrix protein	600310
Pseudohypoparathyroidism, type Ia, 103580 (3)	20q13.2	GNAS1, GNAS, GPSA	Guanine nucleotide-binding protein (G protein), alpha-stimulating activity polypeptide-1	139320
Pycnodysostosis (2)	1q21	PKND	Pyknodysostosis (pycnodysostosis)	265800
Renal tubular acidosis-osteopetrosis syndrome (3)	8q22	CA2	Carbonic anhydrase II	259730
Rubenstein-Taybi syndrome, 180849 (3)	16p13.3	CREBBP, CBP, RSTS	CREB binding protein	600140
Russell-Silver syndrome (2)	17q25	RSS	Russell-Silver syndrome	180860
Saethre-Chotzen syndrome (2)	7p21	ACS3, SCS	Acrocephalosyndactyly-3 (Saethre-Chotzen syndrome)	101400
Sanfilippo syndrome, type B (3)	17q21	NAGLU	N-acetylglucosaminidase, alpha-	252920
?Sanfilippo syndrome, type C (2)	Chr.14	MPS3C	Mucopolysaccharidosis, type IIIC	252930
Sanfilippo syndrome, type D (1)	12q14	GNS, G6S	N-acetylglucosamine-6-sulfatase	252940
SED congenita (3)	12q13.11-q13.2	COL2A1	Collagen, type II, alpha-1 polypeptide	120140
Severe combined immunodeficiency due to ADA deficiency (3)	20q13.11	ADA	Adenosine deaminase	102700
SMED Strudwick type (3)	12q13.11-q13.2	COL2A1	Collagen, type II, alpha-1 polypeptide	120410
Somatotrophinoma (3)	20q13.2	GNAS1, GNAS, GPSA	Guanine nucleotide-binding protein (G protein), alpha-stimulating activity polypeptide-1	139320
Split hand/foot malformation, type 2 (2)	Xq26	SHFM2, SHFD2	Split hand/foot malformation, type (ectrodactyly) 2	313350
Split-hand/split-foot malformation, type 1 (2)	7q21.2-q21.3	SHFM1, SHFD1, SHSF1	Split hand/foot malformation, type 1	183600
Spondyloepiphyseal dysplasia tarda (2)	Xp22.2-p22.1	SEDL, SEDT	Spondyloepiphyseal dysplasia, late	313400
Stickler syndrome, type I (3)	12q13.11-q13.2	COL2A1	Colalgen, type II, alpah-1 polypeptide	120140
Stickler syndrome, type II, 184840 (3)	6p21.3	COL11A2	Collagen XI, alpha-2 polypeptide	120290
Symphalangism, proximal (2)	17q21-q22	SYM1	Symphalangism 1 (proximal)	185800
Syndactyly, type II (2)	2q31	SPD	Syndactyly type II (synpolydactyly)	186000
Thanatophoric dwarfism, 187600 (3)	4p16.3	FGFR3, ACH	Fibroblast growth factor receptor-3	134934
Treacher Collins mandibulofacial dysostosis (2)	5q32-q33.1	TCOF1, MFD1	Treacher Collins-Franceschetti syndrome-1	154500
Trichorhinophalangeal syndrome, type I (2)	8q24.12	TRPS1	Trichorhinophalangeal syndrome, type I	190350
Triphalangeal thumb-polysyndactyly syndrome (2)	7q36	TPT1	Triphalangeal thumb-polysyndactyly syndrome	190605
Wagner syndrome, type II (3)	12q13.11-q13.2	COL2A1	Collagen, type II, alpha-1 polypeptide	120140

*See OMIM under the entry identified by the six-digit MIM number for information on the clinical, genetic, and molecular features of each disorder. The "(3)" after the name of the disorder means that point mutations have been identified as the basis of the disorder and are listed as "allelic variants" subentries in the primary entry in OMIM. ("1" refers to mapping through the wildtype gene; "2" refers to mapping of the clinical phenotype.)

such as those due to mutation in the GH1 gene itself or in the PIT1, GHRHR, or GHR genes. However, we have included Cockayne syndrome, Rubinstein–Taybi syndrome, and Russell–Silver syndrome.

It turns out that all chromosomes except 13, Y, and the mitochondrial chromosome are the site of the gene mutation responsible for at least one skeletal dysplasia.

Mapping studies of skeletal dysplasias have uncovered some striking examples of heterogeneity: in multiple exostoses, chondrodysplasia punctata, multiple epiphyseal dysplasia, Stickler syndrome, most of the Sillence types of osteogenesis imperfecta, Bardet–Biedl syndrome, and some others. Once heterogeneity is recognized, phenotypic distinctions may be discernible.

Also very striking is the converse: demonstration that clinically disparate disorders are the result of mutation in the same gene. One example is represented by the cluster ("allelic series") of disorders due to various mutations in the gene for type II collagen (COL2A1). The relatedness of this cluster and of others was predicted by Spranger, mainly on radiologic and other phenotypic similarities. One form of multiple epiphyseal dysplasia and pseudoachondroplasia turn out to be allelic disorders due to mutation in the COMP gene. Rivaling the COL2A1 cluster is the group of disorders due to allelic mutations in the FGFR3 gene: achondroplasia, hypochondroplasia, thanatophoric dysplasia, with or without cloverleaf skull, and even Crouzon syndrome with acanthosis nigricans. The allelic series related to the COL1A1 and COL1A2 genes include disorders as disparate as osteogenesis imperfecta and EDS VII.

The only skeletal dysplasia in which the mutant gene was tracked down purely by positional cloning is diastrophic dysplasia. The gene that was isolated by positional cloning was found to encode a sulfate transporter.

Several other skeletal dysplasias, including Marfan syndrome and achondroplasia, are successful examples of the positional candidate gene approach. The FGFR3 gene that is mutant in achondroplasia was found in the course of positional cloning of the Huntington disease gene and because of its expression in cartilage (and brain) was a plausible candidate for achondroplasia when that disorder was found to map to the same region at the tip of the short arm of chromosome 4.

The candidate gene approach involves mutation search in a gene that plausibly is implicated, without any knowledge of whether the disorder phenotype and the gene map to the same chromosomal location. In the list given here, skeletal dysplasias that were molecularly characterized by a candidate gene approach include one form of Stickler syndrome and the Schmid type metaphyseal chondrodysplasia. These disorders were shown to have mutations in collagen genes COL2A1 and COL10A1, respectively, before mapping of the disease phenotype. These genes came under suspicion because both are expressed in cartilage; COL2A1 is also expressed in the ocular vitreous and inner ear, both of which are affected in Stickler syndrome. Note the distinction between candidate gene approach and positional candidate gene approach.

Elucidation of the molecular defect in some skeletal disorders has contributed to basic biologic understanding. For example, finding the defective gene in campomelic dysplasia with autosomal sex reversal uncovered an important step in sex differentiation. The defects in the several different fibroblast growth factor receptors has opened up a new aspect of developmental biology.

The accompanying tables give a chromosome-by-chromosome listing of the gene loci involved in skeletal dysplasias (Table IA) and an alphabetized list of the skeletal dysplasias that have been mapped (Table IB).

The master table (IA) gives for each locus, in separate fields, left–to–right, the chromosomal location, gene symbol, locus name, MIM number, [McKusick, 1994] for the locus, disorders due to mutations at that locus, and the chromosomal localization of the homologous locus in the mouse.

In the disorder field, the name of the disorder is followed by a six–digit MIM number when a description of the phenotype is given in an entry separate from that related to the specific locus. Usually this indicates that mutation at more than one gene locus can produce the given phenotype.

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After the name of each disorder in the disorder field there is a "(1)", "(2)", or "(3)". "(1)" means that the disorder is known to map at the given locus solely because the wildtype ("normal") gene that encodes the protein thought to be defective or deficient maps there. "(2)" means that the disorder phenotype has been mapped to the given location without knowledge of the nature of the gene. (These are candidates for map–based gene discovery.) "(3)" indicates that in addition to being mapped through the wildtype gene and/or through the disorder phenotype, specific mutations causing the disorder have been identified. In OMIM these mutations are individually described in subentries (designated "Allelic Variants") under the appropriate primary entries for the given locus.

Information (with appropriate bibliographic references) on the gene map, the mapping of disorders, and the disorders themselves is available in the continuously updated catalog of human genes and genetic disorders OMIM, the online version of Mendelian Inheritance in Man (MIM). The print version of MIM has appeared in 11 editions, first in 1966 and most recently in 1994 [McKusick, 1994]. OMIM has been publicly available beginning in September 1987. Since December 1, 1995, it has been distributed from the National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD.

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