American Journal of Medical Genetics (Semin. Med. Genet.) 106:282–293 (2001)

ARTICLE

# Molecular-Pathogenetic Classification of Genetic Disorders of the Skeleton

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Genetic disorders of the skeleton (skeletal dysplasias and dysostoses) are a large and disparate group of diseases whose unifying features are malformation, disproportionate growth, and deformation of the skeleton or of individual bones or groups of bones. To cope with the large number of different disorders, the ''Nosology and Classification of the Osteochondrodysplasias,'' based on clinical and radiographic features, has been designed and revised periodically. Biochemical and molecular features have been partially implemented in the Nosology, but the rapid accumulation of knowledge on genes and proteins cannot be easily merged into the clinical–radiographic classification. We present here, as a complement to the existing Nosology, a classification of genetic disorders of the skeleton based on the structure and function of the causative genes and proteins. This molecular–pathogenetic classification should be helpful in recognizing metabolic and signaling pathways relevant to skeletal development, in pointing out candidate genes and possible therapeutic targets, and more generally in bringing the clinic closer to the basic science laboratory and in promoting research in this field. 

**KEY WORDS:** skeleton; genetic disorders; molecular classification; pathogenic classification

## INTRODUCTION

Genetic disorders of the skeleton are a group of disorders with diverse manifestations. Although individually rare, the many different forms add to produce a significant number of affected individuals with significant morbidity and mortality. Clinical manifestations include short stature, malformation, and deformation. The clinical severity differs between individuals, ranging from minor handicaps to death in the neonatal period. In surviving patients, secondary complications of skeletal deformity and manifestations in extraskeletal organs add to the burden of disease.

The complexity of skeletal–genetic phenotypes has been long appreciated. Although single entities have been described in the nineteenth or in the first half of the twentieth century, most individual entities we know today have been delineated much more recently. The criteria used for distinction and classification of genetic skeletal disorders have been clinical features such as growth, age at onset of growth retardation, presence and nature of altered body proportions, and, because of the outstanding role of radiography in defining skeletal disease, radiographic criteria. The mode of genetic transmission and specific extra skeletal abnormalities have also been used. Biochemical data have been incorporated as they became available. Based on this combination of criteria, more than 200 nosologic entities are distinguished currently.

***The criteria used for distinction and classification of genetic skeletal disorders have been clinical features such as growth, age at onset of growth retardation, presence and nature of altered body proportions, and, because of the outstanding role of radiography in defining skeletal disease, radiographic criteria.***

The ''Nomenclature and Classification of the Osteochondrodysplasias'' has been a valuable instrument in defining existing entities and delineating new ones. In the 1992 revision [Spranger, 1992], the classification was oriented toward radiodiagnostic and morphologic criteria and grouped morphologically similar disorders into ''families'' of

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Grant sponsor: Swiss National Science Foundation; Grant number: 31-57272.99; Grant sponsor: USPHS NIH.; Grant number: HD 22657; Grant sponsor: The Hartmann-Müller Foundation.

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DOI 10.1002/ajmg.10233

disorders based on presumed pathogenetic similarities. In the 1997 revision [International Working Group on Constitutional Diseases of Bone, 1998], the families of disorders were to some extent rearranged based on new etiopathogenetic information concerning the gene and/or protein defect in these disorders. Those disorders in which the basic defect was well documented were regrouped into distinct families based on mutations in the same gene (e.g., the achondroplasia group, the type 2 collagen group, the diastrophic dysplasia group). The Nomenclature was focused on the osteochondrodysplasias (as developmental disorders of chondro-osseous tissue) but neglected the classification of the dysostoses (malformations of individual bones or groups of bones), although certain dysostoses (e.g., brachydactyly C) were included because they were caused by mutations in genes associated with dysplasias. The 1997 revision did, however, come with the comment that "with the rapid evolution of our knowledge concerning developmental genes in man, the dysostosis group of disorders is in dire need of reclassification" [International Working Group on Constitutional Diseases of Bone, 1998].

In the 2001 revision,[1] the dysostoses have been reviewed and incorporated in the Nomenclature, which has been called Nosology [Hall, 2002]. At the same time, the Working Group believed that the Nomenclature was becoming a hybrid that would not meet clinical criteria (for example, grouping entities such as achondrogenesis 2 and Stickler syndrome, which are clinically very different, because of their common origin in the *COL2A1* gene) but also would not fully reflect genetic–molecular criteria, because those disorders with unknown defect were still grouped by radiographic criteria. The genetic community might therefore be better served with distinct classifications (Fig. 1): the Nosology as a catalog of defined entities (a sort of master book); a clinical classification, focused on age-specific presentations and clinical signs, to be of help in the diagnostic approach; and a molecular–pathogenetic classification based on affected genes and pathogenetic mechanisms. Ultimately, they can be cross-correlated in an electronic database. Books and computer programs using a gamut of radiographic signs are already widely used [Hall and Shaw, 1994; Taybi and Lachman, 1996]. In this article, we present a classification of genetic disorders of the skeleton based on structure and function of the responsible genes and proteins (Table I).

[1]The Nosology Committee of the International Skeletal Dysplasia Society met in Oxford on Sept. 4 and 5, 2001, under the presidency of Dr. Christine Hall.

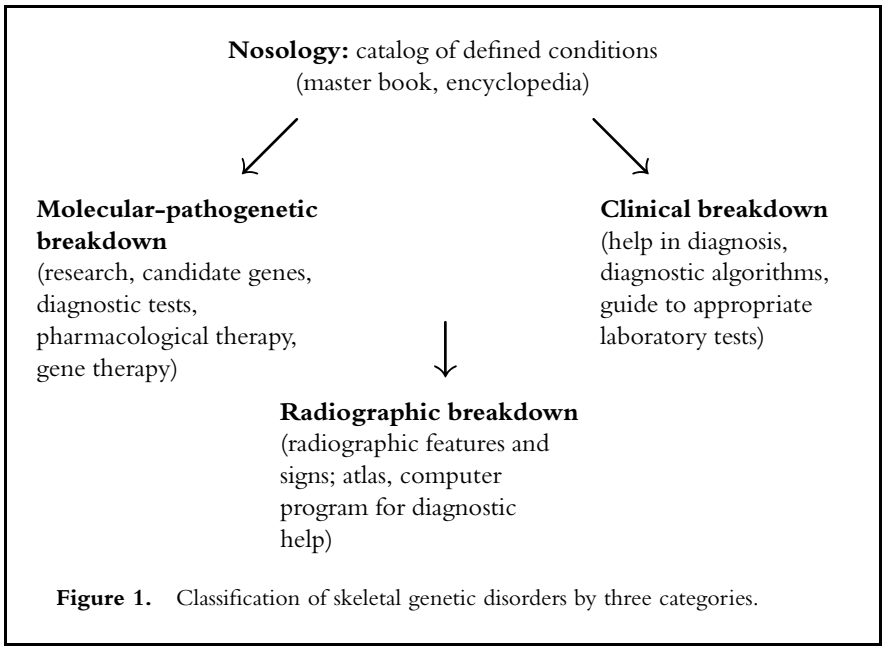


**Figure 1.** Classification of skeletal genetic disorders by three categories.

***In the 2001 revision, the dysostoses have been reviewed and incorporated in the Nomenclature, which has been called Nosology.***

## MOLECULAR–PATHOGENETIC CLASSIFICATION AS A WORKING INSTRUMENT

The accumulation of knowledge on genes and proteins responsible for genetic disorders of the skeleton is unprecedented and has turned the skeletal system into a unique biologic model. The multitude and variety of genes and proteins calls for a molecular and pathogenetic classification. Such a classification should assist in the following purposes:

- To identify metabolic pathways active in cartilage and bone, and their regulatory mechanisms.
- To identify cellular signaling networks and gene expression sequences implicated in skeletal development.
- By the above mechanisms, to identify other elements in those systems as candidate genes for genetic disorders.
- To facilitate integration of data coming from spontaneous and genetically engineered mouse mutants.
- To help in developing diagnostic strategies.
- To stimulate the design and exploration of new therapeutic possibilities.
- To provide a knowledge framework accessible to physicians as well as to basic scientists and thus to facilitate communication between clinical genetics and pediatrics and the basic sciences.

We tried to use classification criteria similar to those used in the functional

**TABLE I. Molecular–Pathogenetic Classification of Genetic Disorders of the Skeleton**

| Gene or protein | Inheritance | Clinical phenotype | References |
|---|---|---|---|
| **Group 1: Defects in extracellular structural proteins** | | | |
| COL1A1, COL1A2 (collagen 1 α1, α2 chains) | AD | *Family*: Osteogenesis imperfecta | Byers, 1990; Prockop et al., 1994 |
| COL2A1 (collagen 2 α1 chain) | AD | *Family*: achondrogenesis 2, hypochondrogenesis, congenital spondyloepiphyseal dysplasia (SEDC), Kniest, Stickler arthro-ophtalmopathy, familial osteoarthritis, other variants | Spranger et al., 1994 |
| COL9A1,COL9A2, COL9A3 (collagen 9 α1, α2, α3 chains) | AD | Multiple epiphyseal dysplasia (MED; two or more variants) | Lohiniva et al., 2000; Spayde et al., 2000 |
| COL10A1 (collagen 10 α1chain) | AD | Metaphyseal dysplasia Schmid | Wallis et al., 1996 |
| Col11A1, Col11A2 (collagen 11 α1, α2 chains) | AR, AD | Oto-spondylo-megaepiphyseal dysplasia (OSMED); Stickler (variant), Marshall syndrome | Melkoniemi et al., 2000; Spranger, 1998 |
| COMP (cartilage oligomeric matrix protien) | AD | Pseudoachondroplasia, multiple epiphyseal dysplasia (MED, one form) | Briggs et al., 1998 |
| MATN3 (matrilin-3) | AD | Multiple epiphyseal dysplasia (MED; one variant) | Chapman et al., 2001 |
| Perlecan | AR | Schwartz-Jampel type 1; dyssegmental dysplasia | Arikawa-Hirasawa et al., 2001 |
| **Group 2: Defects in metabolic pathways (including enzymes, ion channels, and transporters)** | | | |
| TNSALP (tissue nonspecific alkaline phosphatase) | AR, AD | Hypophosphatasia (several forms) | Mornet et al., 1998 |
| ANKH (pyrophosphate transporter) | AD | Craniometaphyseal dysplasia | Nurnberg et al., 2001; Reichenberger et al., 2001 |
| DTDST/SLC26A2 (diastrophic dysplasia sulfate transporter) | AR | *Family*: achondrogenesis 1B, atelosteogenesis 2, diastrophic dysplasia, recessive multiple epiphyseal dysplasia (rMED) | Rossi and Superti-Furga, 2001; Superti-Furga et al., 1996a; Superti-Furga et al., 1996b |
| PAPSS2, phosphoadenosine-phosphosulfate-synthase 2 | AR | Spondylo-epi-metaphyseal dysplasia Pakistani type | ul Haque et al., 1998 |
| TCIRGI, osteoblast proton pump subunit | AR | Severe infantile osteopetrosis | Frattini et al., 2000 |
| CIC-7 (chloride channel 7) | AR | Severe osteopetrosis | Kornak et al., 2001 |
| Carboanhydrase II | AR | Osteopetrosis with intracranial calcifications and renal tubular acidosis | Venta et al., 1991 |
| Vitamin K-epoxide reductase complex | AR | Chondrodysplasia punctata with vitamin K-dependent coagulation defects | Oldenburg et al., 2000; Pauli, 1988; Pauli et al., 1987 |
| MGP (matrix Gla protein) | AR | Keutel syndrome (pulmonary stenosis, brachytelephalangism, cartilage calcifications and short stature) | Munroe et al., 1999 |
| ARSE (arylsulfatase E) | XLR | X-linked chondrodysplasia punctata (CDPX1) | Franco et al., 1995 |
| 3-β-hydroxysteroid-dehydrogenase | XLD | CHILD syndrome | Konig et al., 2000 |
| 3-β-hydroxysteroidΔ(8)Δ(7)-isomerase | XLD | X-linked chondrodysplasia punctata, Conradi-Hünermann type (CDPX2); CHILD syndrome | Braverman et al., 1999; Grange et al., 2000 |
| PEX7 (peroxisomal receptor/importer) | AR | Rhizomelic chondrodysplasia punctata 1 | Motley et al., 1997 |

**TABLE I. (*Continued*)**

| Gene or protein | Inheritance | Clinical phenotype | References |
|---|---|---|---|
| DHAPAT (Di-hydroxy-acetonphosphate-acyltransferase, peroxisomal enzyme) | AR | Rhizomelic chondrodysplasia punctata 2 | Ofman et al., 1998 |
| Alkyl-di-hydroxy-diacetonphosphate synthase (AGPS; peroxisomal enzyme) | AR | Rhizomelic chondrodysplasia punctata 3 | de Vet et al., 1998 |
| **Group 3: Defects in folding and degradation of macromolecules** | | | |
| Sedlin (endoplasmic reticulum protein with unknown function) | XR | X-linked spondyloepiphyseal dysplasia (SED-XL) | Gedeon et al., 1999 |
| Cathepsin K (lysosomal proteinase) | AR | Pycnodysostosis | Hou et al., 1999 |
| Lysosomal acid hydrolases and transporters (sulfatase, glycosidase, translocase, etc.) | AR, XLR | Lysosomal storage diseases: mucopolysaccharidoses, oligosaccharidoses, glycoproteinoses (several forms) | Leroy and Wiesmann, 1993 |
| Targeting system of lysosomal enzymes (GlcNAc-1-phosphotransferase) | AR | Mucolipidosis (II (I-cell disease), mucolipidosis III | Leroy and Wiesmann, 1993 |
| MMP2 (matrix metalloproteinase 2) | AR | Torg type osteolysis (nodulosis arthropathy and osteolysis syndrome) | Martignetti et al., 2001 |
| **Group 4: Defects in hormones and signal transduction mechanisms** | | | |
| 25-α-hydroxycholecalciferol-1-hydroxylase | AR | Vitamin D-dependent rickets type 1 (VDDR1) | Kitanaka et al., 1998 |
| 1,25-α-dihydroxy-vitamin D3 receptor | AR | Vitamin D-resistant rickets with end-organ unresponsiveness to vitamin D3 (VDDR2) | Hughes et al., 1988 |
| CASR (calcium "sensor"/receptor) | AD | Neonatal severe hyperparathyroidism with bone disease (if affected fetus in unaffected mother); familial hypocalciuric hypercalcemia | Bai et al., 1997 |
| PTH/PTHrP receptor | AD (activating mutations) | Metaphyseal dysplasia Jansen | Schipani et al., 1996 |
| | AR (inactivating mutation) | Lethal dysplasia Blomstrand | Zhang et al., 1998 |
| GNAS1 (stimulatory Gs alpha protein of adenylate cyclase) | AD | Pseudohypoparathyroidism (Albright hereditary osteodystrophy and several variants) with constitutional haploinsufficiency mutations; McCune-Albright syndrome with somatic mosaicism for activating mutations | Patten et al., 1990 |
| PEX proteinase | XL | Hypophosphatemic rickets, X-linked semidominant type (impaired cleavage of FGF23) | The HYP Consortium, 1995; Sabbagh et al., 2000 |
| FGF23, fibroblasts growth factor 23 | AD | Hypophosphatemic rickets, autosomal dominant type (resistance to PEX cleavage) | The ADHR Consortium, 2000 |
| FGFR1 (fibroblast growth factor receptor 1) | AD | Craniosynostosis syndromes (Pfeiffer, other variants) | Wilkie, 1997 |
| FGFR2 | AD | Craniosynostosis syndromes (Apert, Crouzon, Pfeiffer; several variants) | Wilkie, 1997 |

**TABLE I. (*Continued*)**

| Gene or protein | Inheritance | Clinical phenotype | References |
|---|---|---|---|
| FGFR3 | AD | Thanatophoric dysplasia, achondroplasia, hypochondroplasia, SADDAN; craniosynostosis syndromes (Crouzon with acanthosis nigricans, Muenke nonsyndromic craniosynostosis) | Passos-Bueno et al., 1999; Wilkie, 1997 |
| ROR-2 ("orphan receptor tyrosine kinase") | AR | Robinow syndrome | Afzal et al., 2000; van Bokhoven et al., 2000 |
| | AD | Brachydactyly type B | Oldridge et al., 2000 |
| TNFRSF11A (receptor activator of nuclear factor kB; RANK) | AD | Familial expansile osteolysis | Hughes et al., 2000 |
| TGFβ1 | AD | Diaphyseal dysplasia (Camurati-Engelmann) | Janssens et al., 2000 |
| CDMP1 (cartilage-derived morphogenetic protein 1) | AR | Acromesomelic dysplasia Grebe/Hunter-Thompson | Thomas et al., 1997; Thomas et al., 1996 |
| | AD | Brachydactyly type C | Polinkovsky et al., 1997 |
| Noggin ("growth factor," TGF antagonist) | AD | Multiple synostosis syndrome; synphalangism and hypoacusis syndrome | Gong et al., 1999 |
| DLL3 (*delta-like 3*, intercellular signaling) | AR | Spondylocostal dysostosis (one form) | Bulman et al., 2000 |
| IHH (Indian hedgehog signal molecule) | AD | Brachydactyly A1 | Gao et al., 2001 |
| C7orf2 (orphan receptor) | AR | Acheiropodia | Ianakiev et al., 2001 |
| SOST (sclerostin; cystine knot secreted protein) | AR | Sclerosteosis, van Buchem disease | Balemans et al., 2001 |
| LRP5 (LDL receptor-related protein 5) | AR | Osteoporosis–pseudoglioma syndrome | Gong et al., 2001 |
| WISP3 (growth regulator/ growth factor) | AR | Progressive pseudorheumatoid dysplasia | Hurvitz et al., 1999 |
| **Group 5: Defects in nuclear proteins and transcription factors** | | | |
| SOX9 (HMG-type DNA binding protein/ transcription factor) | AD | Campomelic dysplasia | Wagner et al., 1994 |
| *Gli3* (zinc finger gene) | AD | Greig cephalopolysyndactyly, polydactyly type A and others, Pallister-Hall syndrome | Kalff-Suske et al., 1999; Radhakrishna et al., 1999 |
| *TRPS1* (zine-finger gene) | AD | Tricho-rhino-phalangeal syndrome (types 1–3) | Momeni et al., 2000 |
| *EVC* (leucine-zipper gene) | AR | Chondroectodermal dysplasia (Ellis-van Creveld) | Ruiz-Perez et al., 2000 |
| TWIST (helix-loop-helix transcription factor) | AD | Craniosynostosis Saethre-Chotzen | el Ghouzzi et al., 1997 |
| P63 (p53 related transcription factor) | AD | EEC syndrome, Hay-Wells syndrome, limby–mammary syndrome, split hand–split foot malformation (some forms) | Celli et al., 1999; McGrath et al., 2001; van Bokhoven et al., 2001 |
| CBFA-1 (core binding factor A1; runt-type transcription factor) | AD | Cleidocranial dysplasia | Mundlos et al., 1997 |
| LXM1B (LIM homeodomain protein) | AD | Nail–patella syndrome | Dreyer et al., 1998 |
| *DLX3* (distal-less 3 homeobox gene) | AD | Trichodentoosseous syndrome | Price et al., 1998 |
| *HOXD13* (homeobox gene) | AD | Synpolydactyly | Akarsu et al., 1996 |
| *MSX2* (homeobox gene) | AD (gain of function) | Craniosynostosis, Boston type | Jabs et al., 1993 |
| | AD (loss of function) | Parietal foramina | Wilkie et al., 2000 |

**TABLE I. (*Continued*)**

| Gene or protein | Inheritance | Clinical phenotype | References |
|---|---|---|---|
| *ALX4* (homeobox gene) | AD | Parietal foramina (cranium bifidum) | Mavrogiannis et al., 2001 |
| *SHOX* (short stature-homeobox gene) | Pseudoautosomal | Léri-Weill dyschondrosteosis, idiopathic short stature? | Shears et al., 1998 |
| TBX3 (T-box 3, transcription factor) | AD | Ulnar–mammary syndrome | Bamshad et al., 1997 |
| TBX5 (T-box 5, transcription factor) | AD | Holt-Oram syndrome | Li et al., 1997 |
| EIF2AK3 (transcription initiation factor kinase) | AR | Wolcott-Rallison syndrome (neonatal diabetes mellitus and spondyloepiphyseal dysplasia) | Delepine et al., 2000 |
| NEMO (NFkB essential modulator; kinase activity) | XL | Osteopetrosis, lymphedema, ectodermal dysplasia and immunodeficiency (OLEDAID) | Doffinger et al., 2001; Smahi et al., 2000 |
| **Group 6:Defects in oncogenes and tumor suppressor genes** | | | |
| EXT1, EXT2 (exostosin-1, exostosin-2; heparan-sulfate polymerases) | AD | Multiple exostoses syndrome types 1, type 2 | Cheung et al., 2001; Duncan et al., 2001; Lind et al., 1998 |
| SH3BP2 (*c-Abl*-binding protein) | AD | Cherubism | Ueki et al., 2001 |
| **Group 7: Defects in RNA and DNA processing and metabolism** | | | |
| RNAse MRP-RNA component | AR | Cartilage–hair–hypoplasia | Ridanpaa et al., 2001 Bonafé et al., 2002 |
| ADA (adenosine deaminase) | AR | Severe combined immunodeficiency (SCID) with (facultative) metaphyseal changes | Hirschhorn, 1995 |

classification of proteins in *S. cerevisiae, C. elegans,* and disease-related human genes and proteins proposed in the 8th edition of *The Metabolic and Molecular Bases of Inherited Disease* [Jimenez-Sanchez et al., 2001]. We also tried to take into account the peculiarities intrinsic to skeletal biology. We grouped molecular defects as follows (Table I).

- *Group 1:* Defects in extracellular structural proteins.
- *Group 2:* Defects in metabolic pathways (including enzymes, ion channels, transporters).
- *Group 3:* Defects in folding, processing, and degradation of macromolecules.
- *Group 4:* Defects in hormones and signal transduction mechanisms.
- *Group 5:* Defects in nuclear proteins and transcription factors.
- *Group 6:* Defects in oncogenes and tumor-suppressor genes.
- *Group 7:* Defects in RNA and DNA processing and metabolism.

Skeletal disorders with a well-documented genetic and biochemical basis have been assigned to one of these groups. The interpretation proposed in the original reports has been used as the basis for classification, and other literature pertinent to the proposed molecular mechanism(s) has been consulted when the original description of the genetic defect fell short of suggesting a plausible pathogenetic mechanism or when new data have been published subsequently. The bibliographic references included are limited to the original description of the molecular defect or, in some cases (e.g., the lysosomal disorders), to review reports; those looking for further details should consult that literature and/or the online version of Mendelian Inheritance in Man, OMIM.

Any attempt to reduce biological complexity into a straightforward classification is forceful. The following remarks should be considered:

- By analogy to the *S. cerevisiae/C. elegans*/MMBID8 classification [Jimenez-Sanchez et al., 2001], a group consisting of skeletal dysplasias caused by defects in *intracellular structural proteins* can be predicted, but none seems to have been identified so far. Secondary cytoskeletal abnormalities occur in chondrocytes from multiple exostoses patients with mutations in *EXT1* and *EXT2* [Bernard et al., 2000]. Similarly, no defects in *ribosomal proteins* have been identified yet (but see the *CHH* gene in group 7).
- Some genes and proteins would fall into two categories: e.g., the heparan glycosyltransferases responsible for the multiple cartilaginous

exostoses syndromes are "metabolic" enzymes, but because of their phenotypic associations they are best classified as tumor-suppressor genes). The reader may recognize further examples.

- The function of some proteins is not known precisely. It is likely that future insights will lead to reclassification.
- This classification is a hybrid between a pathogenetic–functional classification and a strictly molecular one. Where the precise function of a gene product is known, or the gene product could be clearly positioned within a metabolic or regulatory pathway, the functional criterion has been given priority over the biochemical and molecular one, to highlight the pathogenetic aspects. Where the pathogenetic context is not known yet, purely molecular criteria have been used.

## EXPLANATION AND COMMENTARY ON THE INDIVIDUAL GROUPS

### Group 1: Defects in Extracellular Structural Proteins (Table I)

This group includes some of the best-characterized dysplasia "families," those of the main bone collagen, collagen 1, and of the main cartilage collagen, collagen 2. Other cartilage collagens are also listed (collagens 9, 10, and 11). The phenotypic manifestations caused by mutations in cartilage collagens are dependent on the tissue expression of the respective genes. The two related proteins, COMP and MATN-3, are believed to serve a bridging function between extracellular matrix proteins. Given the role of proteoglycans in the cartilage matrix, the presence of only a single proteoglycan, perlecan, in this list is surprising. The gene coding for the core protein of aggrecan, the most abundant cartilage proteoglycan, remains a candidate for this group, as do the genes for several other proteoglycans and glycoproteins. Absence of several noncollagenous proteins of bone is also notable. If compared to the other groups, the impression arises that the number of different "raw materials" used in skeletal development and growth is comparatively small, but this simply may be reflecting the current state of our knowledge, and further research may disprove this.

***The phenotypic manifestations caused by mutations in cartilage collagens are dependent on the tissue expression of the respective genes. The two related proteins, COMP and MATN-3, are believed to serve a bridging function between extracellular matrix proteins.***

### Group 2: Defects in Metabolic Pathways (Including Enzymes, Ion Channels, and Transporters)

The emergence of pathways whose function is essential for proper skeletal development is clearly recognizable in this group. Two proteins (TNSALP, and the pyrophosphate transporter ANKH); are involved in phosphate and/or pyrophosphate metabolism and thus in mineralization; the existence of another disorder, IACI [Rutsch et al., 2001], featuring ectopic calcification and related to pyrophosphate deficiency points to a complex pathway. These three disorders would not have been related to each other on a phenotypic level. Two proteins are involved in sulfate metabolism (the sulfate transporter, DTDST and the PAPS-synthetase, PAPSS2); other enzymes of this pathway, particularly the sulfotransferases, are candidates for other disorders. Three proteins are involved in acidification of the osteoclast ruffle border (TCIRG2; ClC7; and carboanhydrase 2); all three are associated with osteopetrosis. The two pathways, "acidification" and "sulfation," appear to justify inclusion of ion channels and ion pumps in the same group as enzymes. Three as yet not completely understood disorders may point to a vitamin K-dependent pathway of calcium regulation: vitamin K epoxide reductase complex (only biochemical evidence so far), matrix GLA protein (MGP; a gamma-carboxylated matrix protein), and arylsulfatase E. The group also includes two peroxisomal enzymes (the two initial enzymes of plasmalogen biosynthesis; the causal link between plasmalogens and calcification is still unclear), and a peroxisomal biogenesis protein (PEX-7) that acts as a receptor and importer for peroxisomal enzymes. Included are also two enzymes of cholesterol biosynthesis. Whether cholesterol biosynthesis defects act pathogenetically through disturbed *hedgehog* signaling, as proposed for the Smith-Lemli-Opitz syndrome, is unclear. Both the peroxisomal and the cholesterol biosynthesis defects are associated with various forms of chondrodysplasia punctata.

***Two proteins are involved in sulfate metabolism (the sulfate transporter, DTDST and the PAPS-synthetase, PAPSS2); other enzymes of this pathway, particularly the sulfotransferases, are candidates for other disorders.***

### Group 3: Defects in Folding, Processing, and Degradation of Macromolecules

The main category of disorders in this group are the lysosomal storage disorders, particularly the mucopolysaccharidoses, which have been among the first skeletal dysplasias to be described and also among the first to be understood at the biochemical level. The individual acid hydrolases and transporters responsible for the mucopolysaccharidoses and glycoproteinoses have not been listed

individually; the Nosology should be consulted for a detailed list [International Working Group on Constitutional Diseases of Bone, 1998; Hall, 2002]. The lysosomal targeting system involves an *N*-acetylglucosamine-1-phosphotransferase activity, the gene(s) for which have still eluded identification. Cathepsin K is so far the only lysosomal proteinase involved in a genetic disorder of the skeleton. Matrix metalloproteinase 2 (MMP2), the single extracellular proteinase in this group, has recently been linked to one of the osteolysis syndromes; because many other matrix proteinases are known, this is an area of potential future expansion. Sedlin is a protein predicted to be resident in the endoplasmic reticulum and as such may be involved in protein folding or protein transport, again a single representative in this group so far.

### Group 4: Defect in Hormones and Signal Transduction Mechanisms[2]

This is a complex and heterogeneous group that includes signaling systems that act at distance (endocrine) as well as others that may act over short distances (paracrine), sometimes as gradients, or even on the same cell where they originate from (autocrine). In addition, although certain mechanisms are functional until adulthood, others may be restricted to the embryonic period. Although this group may appear to be too heterogeneous, it is difficult to draw clear separation lines at present, and we suggest that the group may be revised in the future.

In the *endocrine subgroup*, a first pathway is defined by vitamin D3 synthesis (1-hydroxylase) and action (vitamin D3 receptor; the bioactive form of vitamin D is generally considered a steroid hormone, and its receptor is related to other steroid receptors). A second pathway involves calcium and the parathyroid hormone (PTH) axis (the calcium sensor CASR, which controls PTH release, and the PTH-related peptide receptor). Downstream in the pathway, the GNAS1 adenylate cyclase subunit is implied in PTH signal transduction (pseudohypoparathyroidism) but may serve other functions as well. A third, recently identified pathway relates to *FGF23* as a phosphaturic hormone: structural mutations in *FGF23* rendering it resistant to cleavage by the PEX proteinase are associated with autosomal-dominant hyperphosphaturic hypophosphatemic rickets, whereas defects in the PEX proteinase, responsible for the much more common X-linked hypophosphatemic rickets, impair cleavage of FGF23.

The *paracrine-autocrine signal systems* in the group comprise secreted proteins with putative growth factor, regulatory, or signaling functions, as well as receptors and membrane signaling proteins. Genes and proteins are grouped here solely because of their involvement in signal transduction, with little consideration (and sometimes little information) regarding the signaling pathways they belong to. Among the secreted proteins are transforming growth factor (TGF)β1, CDMP-1 (a member of the TGFβ superfamily), and a TGFβ antagonist, *noggin*. Another secreted protein, SOST, appears to be a regulator of new bone deposition during the whole life span (but when mutated may also cause syndactyly). A further secreted protein, WISP3, appears to be a requisite for cartilage trophism, its absence leading to severe cartilage degeneration. The absence of any FGF from this group so far is notable (but see *FGF23*, above). Two proteins, IHH and DLL3, may function both as diffusible and as cell membrane–associated receptors or ligands: IHH, a member of the hedgehog family, is cleaved into a membrane-associated and a diffusible fragment. DLL3 (delta-like 3) is cell associated but is itself a ligand ("transmembrane ligand") for another membrane receptor, *notch*. On the receptor side are the receptor tyrosine kinases FGFR1, FGFR2, and FGFR3 (that are responsible for a number of relatively frequent disorders) and ROR2. C7orf2 is a putative receptor whose ligand is not known; it may act by repressing sonic hedgehog; its function is crucial because its absence results in acheiropodia (absence of hands and feet). The RANK receptor, a member of the TNF receptor superfamily, has been implicated in osteoclast differentiation and response to PTH as well as to osteoprotegerin ligand; activating mutations have been associated with expansile osteolysis (inactivating mutations result in osteoporosis in the mouse). The recently identified LDR5, related to lipoprotein receptors, is involved in a signaling pathway controlling bone mass. Finally, it is notable that for *CDMP-1* and *ROR2*, distinct phenotypes associated with either heterozygosity or homozygosity for mutations are known; in both cases, the heterozygous state is a form of brachydactyly, whereas the homozygous state results in more severe phenotypes.

***The paracrine-autocrine signal systems in the group comprise secreted proteins with putative growth factor, regulatory or signaling functions, as well as receptors and membrane signaling proteins. Genes and proteins are grouped here solely because of their involvement in signal transduction, with little consideration (and sometimes little information) regarding the signaling pathways they belong to.***

### Group 5: Defects in Nuclear Proteins and Transcription Factors

This is a group assembled purely on structural features of the proteins rather than by pathways (although for some factors, such as Gli3, connected regulatory pathways are known). DNA-bind-

[2]Defects in growth hormone (hGH), the hGH receptor, and in the IGF pathways have not been included because they produce short stature but are not considered genetic disorders of the skeleton; they are not included in the Nosology either.

ing motifs such as HMG (SOX9), zinc finger (GLI3 and TRPS), leucine zipper (EvC), helix–loop–helix (TWIST), homeodomains or homeoboxes (LXM1B, HOXD13, MSX2, ALX4, and SHOX), T-boxes (TBX3, TBX5), runt domain (CBFA1), or p53-related domain (p63) characterize the genes and proteins grouped here. Many of the associated phenotypes are dysostoses rather than generalized dysplasias, lending support to the general concept of dysostoses being caused by embryonic developmental errors as opposed to dysplasias that exert their effect acting during the whole period of skeletal growth. There are two exceptions: both the EIF2AK3 (transcription initiation factor kinase) and the *NEMO* (NFkB essential modulator) gene are not transcription factors themselves but kinases that phosphorylate and activate transcription factors. Interestingly, mutations in both of these genes produce pleiotropic phenotypes (diabetes, liver disease, and spondyloepiphyseal dysplasia in the Wolcott-Rallison syndrome; osteopetrosis, ectodermal dysplasia and immunodeficiency in males, and incontinentia pigmenti in females with NEMO mutations).

### Group 6: Defects in Oncogenes and Tumor-Suppressor Genes

*EXT1* and *EXT2* are the two genes responsible for the multiple cartilaginous exostoses syndromes types 1 and 2. Both code for membrane-associated endoplasmic reticulum proteins with D-glucuronic acid (GlcA) and *N*-acetylglucosamine (GlcNAc) transferase activities representative of a heparan sulfate-polymerase; the two proteins are colocalized and probably heteromultimeric. Their phenotypic effects as well as a series of cell biology experiments have highlighted the role of heparan sulfate proteoglycans in cell differentiation and tumor genesis, prompting their classification as tumor-suppressor genes. The *SH3BP2* gene codes for a still ill-defined protein that may have affinity to the oncogene *c-Abl*. Activating mutations are found in individuals with cherubism, a disorder with locally dysregulated bone overgrowth. The *SH3BP2* gene can thus be tentatively classified as an oncogene. The Nosology comprises several other disorders with disorganized development of cartilage and fibrous tissues; it will be of interest to see whether common pathways exist or whether disorganized expression may arise from mutations in genes from different pathways.

***EXT1 and EXT2 are the two genes responsible for the multiple cartilaginous exostoses syndromes types 1 and 2. Both code for membrane-associated endoplasmic reticulum proteins.***

### Group 7: Defects in RNA and DNA Processing and Metabolism

This group is justified essentially by the special features of the cartilage-hair hypoplasia gene, the *RMRP* gene coding for the RNA part of MRP-RNAse. Mutations in what may be a widely expressed housekeeping gene is in accordance with the clinical pleiotropism of cartilage-hair hypoplasia, but little is known about the pathogenesis. Adenosine deaminase (ADA) is an enzyme responsible for purine salvage, and following structural criteria it should be placed in group 2 together with other enzymes, but the pathogenesis of skeletal changes in ADA deficiency does not appear to be directly related to cartilage or bone metabolism. Instead, the combination of metaphyseal changes with immunodeficiency may point to a pathogenetic pathway common to CHH, perhaps involving RNA turnover. Therefore, we tentatively placed it in this group 7.

## CONCLUSIONS

The classification was attempted to identify metabolic pathways, signaling cascades, and regulatory networks. After its completion, it becomes clear that many black holes exist, and many more genes and proteins still have to be discovered. The classification will have to be revised as more pieces will become available. We will be grateful to readers for pointing out omissions, inaccuracies, and errors.

At the present stage, the classification can be compared to the reconstruction of a mosaic where many pieces are missing and only partial fragments of the big picture start to become visible (or, perhaps more appropriately, like a reconstruction of a dinosaur's skeleton with only a few bones available). Despite these shortcomings, we hope that the classification may be useful to stimulate thoughts, discussions, and research.

## ACKNOWLEDGMENTS

We thank Dr. Christine Hall and the Members of the Nosology Committee of the International Skeletal Dysplasia Society for their input, and Drs. Dan Cohn, Debbie Krakow, Sheila Unger, and Bill Wilcox who also reviewed the manuscript.

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