The Skeletal Dysplasias

Clinical–Molecular Correlations

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ABSTRACT: The skeletal dysplasias or osteochondrodysplasias are a clinically and genetically heterogeneous group of disorders of bone and/or cartilage. They are characterized by abnormalities in pattering, linear growth, differentiation, and maintenance of the human skeleton. While they have been considered to be generalized disorders of endochondral and/or membranous ossification, the extent of their clinical and molecular heterogeneity is still being elucidated. In the 2006 revision of the International Nosology and Classification of Genetic Skeletal Disorders, 372 different conditions were listed in 37 groups defined by such molecular, biochemical, and/or radiographic criteria. The evaluation of patients with chondrodysplasias mandates a multidisciplinary approach involving clinical geneticists, radiologists, molecular biologists, and biochemical geneticists for diagnosis, and a host of surgical specialists for management of their many complications. Our International Skeletal Dysplasia Registry is a worldwide referral center for the skeletal dysplasias, and we have received cases from over 3000 physicians from 50 different countries and have been involved in the identification of the molecular defect in over 40 disorders involving over 25 different genes. Instructions on accessing the Registry, using the diagnostic services provided and contributing cases for collaborative research can be found at www.csmc.edu/skeletaldysplasia.

KEYWORDS: skeletal; dysplasia; dysostosis; dwarf

The skeletal dysplasias or osteochondrodysplasias are a clinically and genetically heterogeneous group of disorders of bone and/or cartilage. They are characterized by abnormalities in pattering, linear growth, differentiation, and maintenance of the human skeleton.[1] These disorders can be divided into

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three main subgroups: osteodysplasias, chondrodysplasias, and dysostoses. The osteodysplasias are generally associated with primary abnormalities in bone leading to alterations in bone density and mineralization, such as osteopenia or osteosclerosis. The chondrodysplasias result from genetic abnormalities affecting cartilage, leading to short stature. The dysostoses have been defined as malformations of individual bones or a group of bones. However, it is now apparent that the distinctions between these subgroups have become blurred, and mutations in individual genes can produce abnormalities in bone, cartilage, and can preferentially affect certain skeletal elements.

Chondrodysplasias generally affect the entire appendicular skeleton and the progressive abnormalities lead to changes in the size and shape of the limbs, trunk, and/or skull, frequently resulting in disproportionate short stature.[2] While they have been considered to be generalized disorders of endochondral and/or membranous ossification, the extent of their clinical and molecular heterogeneity is still being elucidated. In the past, most disproportionate dwarfs were referred to as having either achondroplasia (i.e., those with short limbs) or Morquio disease (i.e., those with short trunks). It is now apparent that there are over 370 distinct skeletal dysplasias, which must be differentiated one from another for specific genetic counseling, prognosis, and treatment. The classification of the skeletal dysplasias was first limited to clinical and radiographic criteria. Indeed, many cases observed today still can only be classified on these grounds and numerous cases still defy classification as an established entity. A need to develop a uniform and consistent nomenclature and classification system for these conditions led to development of the "International Nomenclatures of Constitutional Diseases of Bone." This was initially formulated in 1972 and the nomenclature has been regularly revised (International Working Group on Constitutional Diseases of Bone). The initial categorizations were purely descriptive and consisted of a mixture of the key clinical, radiographic, and pathologic features of each condition. The concept of grouping disorders with similar clinical and radiographic abnormalities then evolved, leading to the concept of *bone dysplasia families*.[3] The most recent classification is a hybrid that incorporates clinical (i.e., mesomelic dysplasia group), radiographic (i.e., metaphyseal dysplasia group), and molecular (i.e., type II collagenopathies group) descriptors, as well as employing various Greek terms (e.g., atelosteogenesis–omodysplasia group) to classify the conditions.[4] In the 2006 revision of the International Nosology and Classification of Genetic Skeletal Disorders, 372 different conditions have been listed in 37 groups defined by such molecular, biochemical, and/or radiographic criteria (TABLE 1[4]) (http://www.isds.ch/ISDSframes.html?=ISDSStatutesGuidelines.html). It is now apparent that no single classification of these disorders will be adequate, necessitating the development of a multidimensional electronic classification tool, incorporating clinical, radiographic, morphologic, biochemical, molecular, and pathway data.

The evaluation of patients with chondrodysplasias mandates a multidisciplinary approach involving clinical geneticists, radiologists, molecular

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TABLE 1. International nosology and classification of genetic skeletal disorders—2006 revision (groups of disorders)

1. FGFR3 group
2. Type 2 collagen group
3. Type 2 collagen group
4. Sulfation disorders group
5. Perlecan group
6. Filamin group
7. Short-rib dysplasia (SRP) (with or without polydactyly) group
8. Multiple epiphyseal dysplasias and pseudoachondroplasia group
9. Metaphyseal dysplasias
10. Spondylometaphyseal dysplasias (SMD)
11. Spondylo-epi(-meta)physeal dysplasias (SE(M)D)
12. Severe spondylodysplastic dysplasias
13. Moderate spondylodysplastic dysplasias (brachyolmias)
14. Acromelic dysplasias
15. Acromesomelic dysplasias
16. Mesomelic and rhizomesomelic dysplasias
17. Bent bones dysplasias
18. Slender bone dysplasias
19. Dysplasias with multiple joint dislocations
20. Chondrodysplasia punctata (CDP) group
21. Neonatal osteosclerotic dysplasias
22. Increased bone density group (without modification of bone shape)
23. Increased bone density group with metaphyseal and/or diaphyseal involvement
24. Decreased bone density group
25. Defective mineralization group
26. Lysosomal storage diseases with skeletal involvement (dysostosis multiplex group)
27. Osteolysis group
28. Disorganized development of skeletal components group
29. Cleidocranial dysplasia group
30. Craniosynostosis syndromes and other cranial ossification disorders
31. Dysostoses with predominant craniofacial involvement
32. Dysostoses with predominant vertebral and costal involvement
33. Patellar dysostoses
34. Brachydactylies (with or without extraskeletal manifestations)
35. Limb hypoplasia–reduction defects group
36. Polydactyly-syndactyly-triphalangism group
37. Defects in joint formation and synostoses

biologists, and biochemical geneticists for diagnosis, and a host of surgical specialists for management of their many complications.[5] A careful clinical examination and detailed radiographic evaluation of the skeleton are the first steps toward an accurate diagnosis. A detailed history (length at birth, growth curves, etc.) and pedigree analysis, followed by anthropometric measurements with special emphasis on body proportions are important. Serial radiographic evaluations are often necessary as some skeletal abnormalities may become evident at a later age.[3,6] For an adult patient, availability of a prepubertal skeletal survey, allowing the evaluation of the epiphyses and metaphyses before epiphyseal closure, is essential for the most accurate diagnostic purposes.

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Ossified epiphyses, which are small and/or irregular for age, suggest an epiphyseal dysplasia. Widened, flared, and/or irregular metaphyses suggest a metaphyseal dysplasia, while a diaphyseal abnormality (widening, cortical thickening, or marrow space expansion) suggests an osteodysplasia. Platyspondyly or vertebral irregularities in combination with the aforementioned findings, indicate a spondylo-epiphyseal dysplasia (SED) or spondylo-epi-meta-physeal dysplasia (SEMD).[6] Determination of the components of the skeleton that are abnormal in size, shape, and mineralization pattern greatly aid in refining the differential diagnoses among the skeletal dysplasias.

Morphologic examination of cartilage and bone should also be a part of the diagnostic work-up when possible.[2] Our morphologic studies have and continue to stimulate new avenues of research. For example, our observation that diastrophic dysplasia, achondrogenesis IB and atelosteogenesis II, although quite distinct clinically, showed similar characteristic histopathologic changes (rings or halos of collagen fibrils around the chondrocytes). This led to the discovery that they were all due to mutations in the diastrophic dysplasia sulfate transporter gene[7,8] and affected posttranslational modification of extracellular matrix proteins. Recognition of the morphological similarities between the Silverman–Handmaker form of dyssegmental dysplasia and the perlecan knockout mouse led to the definition of the first known mutation in the human *Perlecan* gene.[9] Histologic studies of atelosteogenesis types I and III and Boomerang dysplasia, which we defined more than 20 years ago, contributed to the definition of defects in filamin B in this group of disorders.[10] In addition to traditional histologic analysis and immunohistochemical techniques, confocal imaging of human chondroosseous tissue is providing new insights into the functions of the proteins encoded by skeletal dysplasia disease genes.[10] Thus patients undergoing surgery should be considered for bone and cartilage specimen collection since the analysis of the morphology can lead to novel insights. Details on the collection and analysis of such specimens can be found at www.csmc.edu/skeletaldysplasia.

During the past decade, enormous progress has been made in our knowledge concerning the biochemical and molecular genetic basis of these disorders.[11] Until recently, the biochemical defect had only been described in a few skeletal dysplasias, such as the lysosomal storage disorders (e.g., the mucopolysaccharidoses, mucopolidoses), peroxisomal diseases (e.g., the rhizomelic form of chondrodysplasia punctata), and various mineralization defects, (e.g., hypophosphatasia, hypophosphatemic rickets, and various form of osteopetrosis).[2] In the 1980s, elucidation of defects in the type I collagen genes in osteogenesis imperfecta paved the way to further assessment of extracellular matrix protein defects in the skeletal dysplasias.[12] Based on the tissue distribution of type II collagen, which is limited to cartilage, the nucleus pulposus of the vertebrae and the vitreous of the eye, our group postulated that the disorders in which these tissues were affected would be likely candidates for type II collagen defects.[13] These disorders include the SEDs, Kniest dysplasia,

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TABLE 2. Molecular–pathogenetic classification of the skeletal dysplasias[a]

Defects in extracellular structural proteins
- COL1A1, COL1A2: Osteogenesis imperfecta
- COL2A1: achondrogenesis 2, hypochondrogenesis, SEDC, SEMD, Kniest, Stickler, familial osteoarthritis
- COL9A1, COL9A2, COL9A3: Multiple epiphyseal dysplasia (MED)
- COL10A1: Metaphyseal dysplasia Schmid
- COL11A1, COL11A2: Oto-spondylo-megaepiphyseal dysplasia (OSMED); Stickler (variant), Marshall syndrome
- COMP: Pseudoachondroplasia, MED
- MATN3: Multiple epiphyseal dysplasia (MED)
- Perlecan: Schwartz-Jampel type 1; dyssegmental dysplasia

Defects in metabolic pathways
- TNSALP (tissue non-specific alkaline phosphatase): Hypophosphatasia (several)
- ANKH (pyrophosphate transporter): Craniometaphyseal dysplasia
- DTDST (diastrophic dysplasia sulfate transporter): achondrogenesis 1B, atelosteogenesis 2, diastrophic dysplasia, autosomal recessive MED (rMED)
- PAPSS2 (phosphoadenosine-phosphosulfate-synthase 2): Spondylo-epi-metaphyseal dysplasia Pakistani type
- CHST3 (chondroitin 6-O-sulfotransferase-1): SEMD Omani type

Defects in folding, processing, transport, and degradation of macromolecules
- Sedlin (unknown function): X-linked Spondyloepiphyseal dysplasia (SED-XL)
- Cathepsin K (lysosomal proteinase): Pycnodysostosis
- Lysosomal acid hydrolases and transporters: Mucopolysaccharidoses, oligosaccharidoses, glycoproteinoses
- Targeting system for lysosomal enzymes (GlcNAc-1-phosphotransferase): Mucolipidosis II & III
- MMP2 (matrix metalloproteinase 2): Torg type osteolysis
- Tubulin chaperonin E: Kenney-Caffey and Sanjod-Sakati syndromes (TBCE)
- EXT1, EXT2: Multiple exostoses syndrome types 1&2
- SH3BP2 (c-*Abl*-binding protein): Cherubism

Defects in hormones, growth factors, receptors, and signal transduction
- FGFR1: Craniosynostosis syndromes (Pfeiffer)
- FGFR2: Craniosynostosis syndromes (Apert, Crouzon, Pfeiffer)
- FGFR3: Thanatophoric dysplasia, achondroplasia, hypochondroplasia, SADDAN; craniosynostosis syndromes
- ROR-2 (“orphan receptor tyrosine kinase”)
- AR-Robinow syndrome
- AD-Brachydactyly type B
- PTH/PTHrP receptor:
  (activating mutations) Metaphyseal dysplasia Jansen
  (inactivating mutation) Blomstrand lethal dysplasia
- GNAS1 (stimulatory Gs α protein of adenylate cyclase): Pseudohypoparathyroidism (Albright Hereditary Osteodystrophy) with constitutional haploinsufficiency mutations
- McCune–Albright syndrome with somatic mosaicism for activating mutations

Defects in nuclear proteins and transcription factors
- SOX9: Campomelic dysplasia
- TRPS1 (zinc-finger gene): Tricho-Rhino-Phalangeal syndromes
- CBFA-1 (runt-type transcription factor): Cleidocranial dysplasia

Continued

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TABLE 2. *Continued*

LXM1B (LIM homeodomain protein): Nail-patella syndrome
SHOX (short stature—homeobox gene): Leri–Weill dyschondrosteosis, Turner syndrome
EVC (Leucine-zipper gene)
AR-Chondroectodermal dysplasia (Ellis-van Creveld)
AD-Weyers acrodental dysostosis
Defects in RNA processing and metabolism
RMRP: Cartilage-hair-hypoplasia
SDDS–Schwachman–Diamond syndrome
Defects in cytoskeletal proteins
Filamin (actin binding proteins):
Filamin A: Otopaltodigfital syndromes I & II; frontometaphyseal dysplasia; Melnick-Needles
Filamin B: Spondylocarpotarsal syndrome; Larsen syndrome; Atelosteogenesis I/III; Boomerang dysplasia
Responsible gene identified, but function unknown
Dymeclin: Dyggve–Melchior–Clausen syndrome; Smith–McCort syndrome

[a]Modified from Superti-Furga *et al.*, 2001[17]

and Stickler syndrome. Subsequently, we described mutations in the type II procollagen gene in a large group of patients with phenotypes ranging from severe achondrogenesis II, to hypochondrogenesis, to the various SEDs and SEMDs, through Kniest dysplasia and the mildest of the disorders, Stickler syndrome.[14] Other investigators have confirmed and expanded on these findings and numerous mutations have been defined in what are now referred to as the "type II collagenopathies."[15] Further, a unique phenotypic spectrum of arg-cys mutations in this gene leading to premature osteoarthritis has recently been defined.[16]

A large number of cartilage extracellular matrix protein defects have now been described in the chondrodysplasias, including abnormalities in types II, IX, X, and XI collagen, matrilin 3, COMP, and perlecan among others. In addition to the class of extracellular (matrix) structural protein defects, the chondrodysplasias can also be pathogenetically grouped into molecular/cellular disorders, which include: defects in metabolic pathways (including enzymes, ion channels, and transporters); defects in folding, processing, transport, and degradation of macromolecules; defects in hormones, growth factors, receptors, and signal transduction; defects in nuclear proteins (transcription factors, homeobox genes); defects in RNA processing and metabolism; and defects in cytoskeletal proteins[17] (TABLE 2). Even though more than 160 skeletal dysplasia/dysostoses disease genes have been identified, there are still a number of disorders in which a locus has been defined within a particular chromosomal region, but the disease gene has not yet been identified. For many more disorders a locus has not yet been identified.

With the identification of the molecular basis of many skeletal dysplasias came the observations that mutations in the same gene can produce quite

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distinct phenotypes, such as lethal achondrogenesis II and mild Stickler syndrome with mutations in *COL2A1*[18] and autosomal dominant Larsen syndrome, atelosteogensis I/III, and autosomal recessive spondylo-carpal-tarsal syndrome with mutations in filamin B.[10] In contrast, similar phenotypes can be produced by mutations in different genes. For example, multiple epiphyseal dysplasia (MED) can result from mutations in six different genes, with the gene involved in about half of the MED cases still waiting to be discovered.[19] In most cases, it is difficult to correlate the precise mutation in a disease gene with the phenotype, making it often impossible to predict the specific phenotype from the molecular data alone (e.g., *COMP* mutations in the phenotypically different pseudoachondroplasia or MED) or the converse, to predict the molecular defect solely from the clinical features seen in an individual (e.g., MED).

Our work in the skeletal dysplasias has been facilitated by the creation of the International Skeletal Dysplasia Registry in 1968. We receive materials on 500–600 cases of these disorders annually and the Registry now contains over 15,000 cases representing almost all forms of skeletal dysplasia. The Registry is a worldwide referral center for the skeletal dysplasias, and we have received cases from over 3000 physicians from 50 different countries who continue to provide us with extensive material for our research. The Registry includes prenatal information, clinical data, radiographs, fixed and frozen chondroosseous tissues, cultured fibroblasts, chondrocytes, and lymphoblastoid cell lines, and/or DNA from many of these patients. Through the activities of the International Skeletal Dysplasia Registry, we have been directly responsible for the original delineation of, or served as a collaborator or provider of essential biological materials for the identification of the molecular defect in over 40 disorders involving over 25 different genes. Instructions on accessing the Registry, using the diagnostic services provided and contributing cases for collaborative research can be found at www.csmc.edu/skeletaldysplasia.

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