CHAPTER X

Skeletal Dysplasias*†

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The human skeleton (from the Greek skeletos, dried up) is a complex organ consisting of 206 bones (126 appendicular, 74 axial, 6 ossicles). It has multiple embryonic origins and serves many key functions including mechanical support for movement, protection of vital organs, and acting as a blood and mineral reservoir. The skeleton consists of 2 tissues—bone and cartilage—and 3 cell types—osteoblast, osteoclast, and chondrocyte. Abnormalities in the development, growth, and maintenance of these components give rise to the many and varied forms of skeletal dysplasias (osteochondrodysplasias) that, collectively, represent a significant burden of disease to our community.[1] This chapter discusses the classification and diagnostic evaluation of these disorders, their molecular genetics, and key management issues.

EMBRYOLOGY OF THE SKELETON

The patterning and architectural arrangement of the skeleton is the process during which the number, size, and shape of the future skel-

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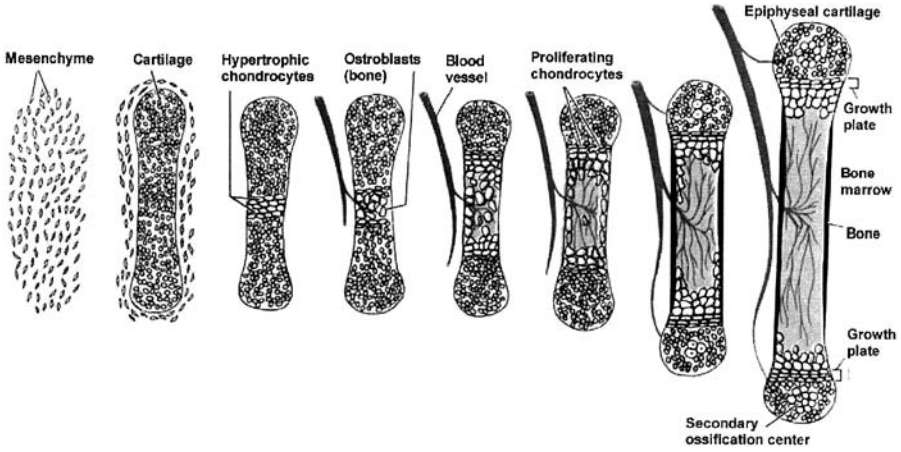

FIGURE 1.
The process of endochondral ossification.

etal elements are determined. This process is under complex genetic control[2] and results in the generation of localized cellular condensations of primitive mesenchyme at the sites of future bone formation (Fig 1). These condensations provide a template (anlagen) for the future bones. Bone formation (skeletogenesis) then occurs by 2 major mechanisms.[3] In the process of *endochondral ossification*, the mesenchyme first differentiates into a cartilaginous model (anlage) of the bone within the condensations. The cartilage in the center of the anlage degrades, mineralizes, and is removed by osteoclast-like cells. This process occurs up and down the length of the bone and allows for vascular ingrowth and influx of osteoprogenitor cells. The periosteum in the midshaft region of the bone produces osteoblasts that begin production of the cortex. This region is known as the primary center of ossification. In the region of the epiphysis (Fig 1), a similar process leading to the removal of cartilage occurs (secondary center of ossification), leaving a portion of cartilage model "trapped" between the expanding primary and secondary ossification centers. This structure is known as the growth plate or physis. The cartilage cells within the growth plate then undergo a tightly regulated program of proliferation, hypertrophy, degradation, and replacement by bone (primary spongiosa). This is the major mechanism of skeletogenesis and the mechanism by which bones increase in length and articular surfaces increase in diameter. The flat bones of the cranial vault and part of the clavicles, in contrast, form by

intramembranous ossification, where fibrous tissue, derived from mesenchymal cells, directly differentiates into osteoblasts, which then lay down bone.[3]

These processes are under specific and complex genetic control,[4-7] and abnormalities of these pathways give rise to the various skeletal dysplasias.

CARTILAGE STRUCTURE

Collagen accounts for two thirds of the dry weight of adult articular cartilage. The collagens are a family of proteins that consist of 3 polypeptide chains wound together in a triple helical structure. Every third amino acid in this triple helix is a glycine residue, and the general chain structure is denoted (Gly-X-Y)n, where X and Y are commonly proline and hydroxyproline. The triple helix can be composed of 3 identical chains (homotrimeric), as seen in collagen type II, or consist of different collagen chains (heterotrimeric), as seen in collagen type XI8.

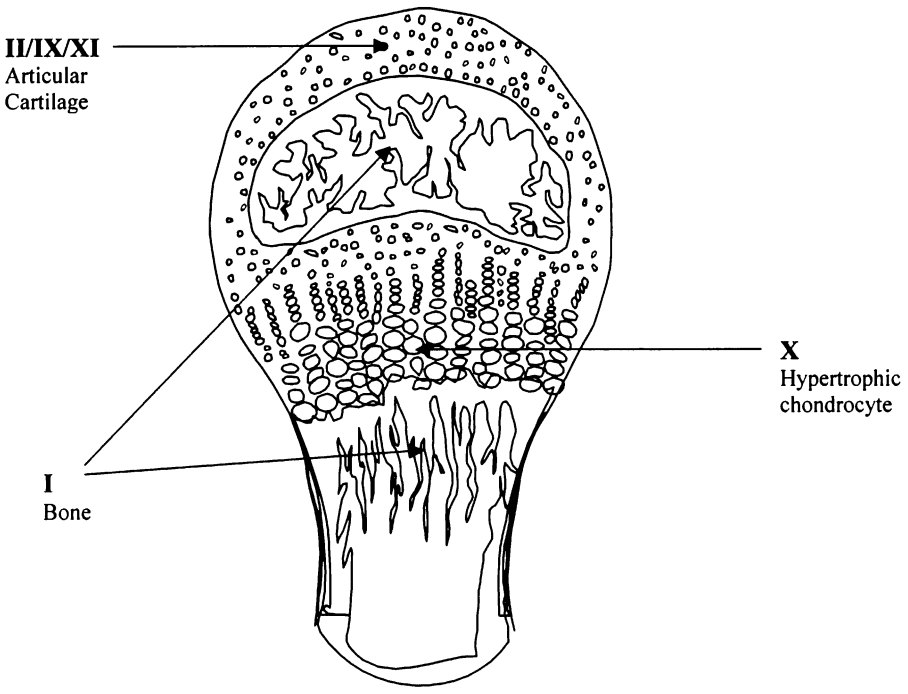

FIGURE 2.
Distribution of collagen types in bone and articular cartilage.

TABLE 1.
Molecular Classification of the Skeletal Dysplasias (Selected Examples)

Defective Molecular Component	Gene/Proteins Involved	Chondrodysplasia Phenotypes
Structural cartilage proteins	Collagen type II	Kniest dysplasia, Stickler syndrome, achondrogenesis type 2
Cartilage metabolic pathways	Diastrophic dysplasia transporter	Diastrophic dysplasia, achondrogenesis IB, atelosteogenesis type 2, recessive multiple epiphyseal dysplasia
Local regulators of cartilage growth	Fibroblast growth factor receptor 3	Achondroplasia, thanatophoric dysplasia, hypochondroplasia
Transcription factors	Short-stature homebox	Dyschondrosteosis, Langer type mesomelic dysplasia
Tumor suppressor genes	Exostosin 1, 2	Multiple hereditary exostoses

Collagens are widely distributed in the body, with 33 currently known collagen genes expressed in a tissue-specific manner, and giving rise to 19 triple helical collagens. Collagens are further classified by the structures they form in the extracellular matrix. The most abundant collagens are the fibrillar types (I, II, III, V, XI), and their extensive cross-linking provides the mechanical strength required in high-stress tissue such as cartilage, bone, and skin.[9] Another collagen species is the fibril-associated collagens with interrupted triple helices (FACIT), comprising collagen types IX, XII, XIV, and XVI. These collagens interact with the fibrillar collagens as well as other extracellular matrix molecules. Collagen types VIII and X are nonfibrillar short-chain collagens, with type X collagen being the most abundant extracellular matrix component synthesized by hypertrophic chondrocytes during endochondral ossification.[10]

The major collagens of articular cartilage are fibrillar collagen types II, XI, FACIT collagen type IX, and the short-chain, nonfibrillar type X collagen (Fig 2). In developing cartilage, the core fibrillar network is a cross-linked copolymer of collagens II, IX, and XI.[9] Collagen type X is restricted to the hypertrophic zone of cartilage (Fig 2). Mutations in genes for these collagens and those encoding other extracellular matrix proteins (ie, matrillin, perlecan) result in various chondrodysplasia phenotypes (Table 1),[B] highlighting the critical importance of these molecules in skeletal development.

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NOSOLOGY AND CLASSIFICATION

Before 1970, disproportionate short stature was viewed as either being "achondroplasia" (short limbed) or "Morquio" disease (short

trunk). Recognition and documentation of the enormous heterogeneity within the skeletal dysplasias necessitated a reappraisal of this simplistic approach. A need to develop a uniform and consistent nomenclature and classification system for these conditions led to the "International Nomenclatures of Constitutional Diseases of Bone." These were initially formulated in 1972 in Paris, and have since been officially revised and updated on 4 occasions (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 recent explosion of molecular genetic techniques in conjunction with the human genome project has allowed the concept of "families" of disorders to evolve, where conditions with similar genetic backgrounds are grouped together. The latest classification is a hybrid that incorporates clinical (ie, mesomelic dysplasia group), radiographic (ie, metaphyseal dysplasia group), and molecular descriptors (ie, type II collagenopathies group), as well as using various Greek terms to classify conditions (ie, atelosteogenesis omodysplasia group). Not surprisingly, attempts to unravel the "logic" of this nomenclature have led to much confusion. At the most recent meeting of the International Working Group (Oxford, September 2001), the need for separate but parallel classifications, one based on clinical presentation and the other on molecular pathogenesis, was clearly identified. The current nomenclature[11] is best regarded as a reference document that gives some structure and classification as well as providing uniform terminology to these numerous conditions. From a practical perspective, accurate diagnosis of these conditions is optimized by thorough clinical and radiographic evaluation.

CLINICAL EVALUATION

HISTORY

An accurate history, including family history, is the foundation upon which the evaluation of any suspected skeletal dysplasia is built. The time of onset of skeletal manifestations in many of these conditions is well defined, and therefore, knowledge of the usual age of presentation is paramount with regards to establishing a diagnosis. Many skeletal dysplasias have a prenatal onset and manifest at birth. Therefore, birth length, weight, and head circumference should be documented. This is especially important in situations where parents (and their physicians) have not appreciated growth failure until early childhood where, in reality, it has been present from birth. In addition, the widespread use of antenatal ultrasound may often

provide clues to diagnosis,[12] and data regarding ultrasound findings and the timing of onset of any abnormalities can be important. For example, the most common skeletal dysplasia that presents at birth is achondroplasia, but abnormal ultrasound findings (ie, short long bones) are not observed until the third trimester of pregnancy. It follows that this condition should not be a serious diagnostic consideration if short limbs are seen at routine 16- to 18-week ultrasound examination. Likewise, a child whose history is that of normal longitudinal growth patterns until the age of 2 years, with subsequent development of disproportionate short stature, is much more likely to have pseudoachondroplasia than achondroplasia or any of the other bone dysplasias with prenatal onset. Diagnosis based purely on age of onset, however, should be tempered by the recognition that some of these disorders do have a wide range of clinical variability (both within and between families). Comprehensive history documentation should also include family history recording by the construction and analysis of a 3-generation pedigree. Unexplained fetal deaths, consanguinity, and other family members with short stature, "orthopedic" problems, or "early arthritis" may provide valuable additional clues to diagnosis or possible mode of inheritance. For example, documentation of male-to-male transmission of a skeletal dysplasia effectively rules out the X-linked conditions, whereas consanguineous parents with several affected children may suggest autosomal recessive inheritance. Specific questioning about parental ages may be relevant, especially in conditions such as achondroplasia and osteogenesis imperfecta in which the mean paternal age is significantly elevated in a high proportion of cases.[13]

PHYSICAL EXAMINATION

Detailed physical examination of the patient as well as parents and other family members may allow definitive diagnosis or narrow diagnostic possibilities to certain groups of conditions. As emphasized above, many skeletal dysplasias present with disproportionate short stature. It is therefore imperative to document current stature with appropriate growth curves,[14,15] as well as plotting any previous anthropometric data (including birth parameters) that are available. This will facilitate analysis of longitudinal growth pattern and the timing of onset of the growth disturbance. Anthropometric measurements taken should include upper-to-lower segment ratio (U/L), sitting height, and arm span.[15] If specific segment shortening is noted on examination (such as short digits), additional measurements (ie, middle finger length, hand length) can be taken to compare against

standardized values.[15] U/L will give an indication of whether disproportionate short stature may be caused primarily by a short trunk (lower than expected U/L) or short limbs (higher than expected U/L). If short limbs are observed, it is important to determine, clinically, whether the shortening primarily affects the proximal (rhizomelic), middle (mesomelic), or distal (acromelic) segments or a combination of these. For example, in achondroplasia (Fig 3), although limb shortening is most pronounced in the rhizomelic segment, there is also significant mesomelic and acromelic shortening. Clinical assessment should also include the craniofacial skeleton and palate. A disproportionately large head with frontal bossing, malar flattening, and depressed nasal bridge is suggestive of achondroplasia or a related condition (ie, hypochondroplasia). Similarly, flattening of the midface with a short nasal columella ("Binder" phenotype) may point to a diagnosis of one of the many types of chondrodysplasia punctata. Other malformations or dysmorphic appearances of the head and neck may provide clues to a specific diagnosis or direct further investigation. Robin sequence (micrognathia and cleft palate) in association with prominence of the eyes and myopia or retinal detachment should lead to suspicion of Stickler syndrome or one of the related type II collagen "family" of disorders.[11] Nontender cystic swelling of the pinnae occurring at 4 to 8 weeks is almost pathognomonic of diastrophic dysplasia in the disproportionately short infant.

Other specific findings can provide clues to diagnosis, and a systematic clinical evaluation should be performed to detect these signs. The hands and feet are particularly important to examine with polydactyly (short-rib polydactyly group), abducted or "hitchhiker" thumbs and great toes (diastrophic dysplasia), dislocated fingers (pseudodiastrophic dysplasia), and dysplastic nails with triangular lunulae (nail-patella syndrome), all indicating potential diagnoses. Cardiac defects can be associated with several of the skeletal dysplasias. In chondroectodermal dysplasia, a common atrium is characteristic,[16] whereas a variety of complex heart lesions can be associated with the short-rib polydactyly disorders.[17] Developmental delay is not usually seen in association with skeletal dysplasias but can be a feature of the mucoplysaccharidoses and Dyggve-Melchior-Clausen dysplasia.[18]

Sometimes, especially in the older child or adult, specific orthopedic complications of the underlying condition may aid with diagnosis. For example, severe deformities at the knees (genu valgum, varum, or a combination of these) associated with ligamentous laxity may be suggestive of pseudoachondroplasia.[19] Likewise, bilat-

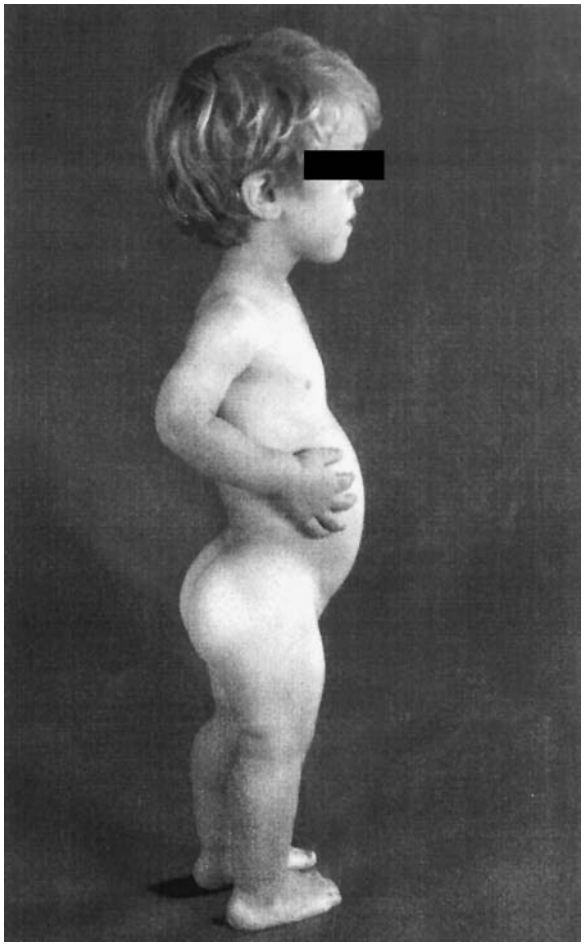

FIGURE 3.
Child with achondroplasia. Note frontal bossing and rhizomelic shortening of upper limbs.

eral abnormalities at the wrists (with dorsal subluxation of the distal ulna) with shortened forearms (Madelung deformity) points to a diagnosis of dyschondrosteosis.[20]

Careful physical examination of parents and siblings of the index case is also important and can provide clues to the diagnosis and also the inheritance pattern. Many conditions that appear to have arisen spontaneously in the index case may have been inherited from a parent who only shows minimal manifestations of the

condition because of variable expression of the disease gene or somatic mosaicism. For example, a child who has multiple bone fractures in whom the diagnosis of osteogenesis imperfecta is suspected may have a parent with a less dramatic history of fractures who, on examination, is found to have blue sclerae and opalescent teeth. This would be a very important finding to document, as it would imply a 1 in 2 (50%) recurrence risk for future children of this parent rather than a much lower risk (7%-8%) if the index case occurred as the result of a new mutation. In parents of patients who have skeletal dysplasias resulting from homozygous gene mutations (ie, Ellis-van Creveld syndrome or Langer mesomelic dysplasia), parents may display the heterozygous manifestations of the condition (ie, Weyers acrodental dysplasia or dyschondrosteosis), and these should be specifically sought.[21,22] Siblings of index cases should also be examined whenever available, as they may also exhibit minor manifestations of the condition that may provide further clues to inheritance pattern and diagnosis.

RADIOGRAPHIC EVALUATION

History and examination, which may lead to a specific diagnosis or focusing of diagnostic considerations, are followed by a thorough radiographic evaluation, which remains the most powerful single tool for diagnosis of the skeletal dysplasias. It is imperative that a complete "genetic" skeletal survey is performed in children older than 6 months (Table 2), to make an accurate diagnosis. In newborns and infants younger than 6 months, anteroposterior and lateral radiographs of the whole body can be performed, but separate anteroposterior films of both hands and a lateral radiograph of the skull should also be obtained.

TABLE 2.
Complete "Genetic" Skeletal Survey for Evaluation of Suspected Skeletal Dysplasia (for a Child Aged 6 Months or Older)

Region	Views Required
Skull	Caldwell, lateral, and Towne 45°
Cervical spine	Lateral, flexion, and extension
Thoracic spine	Anteroposterior and lateral
Lumbar spine	Anteroposterior and lateral
Pelvis and hips	Anteroposterior
Chest	Anteroposterior (rib technique)
Hands and feet	Anteroposterior (include wrists)
Long bones	Anteroposterior

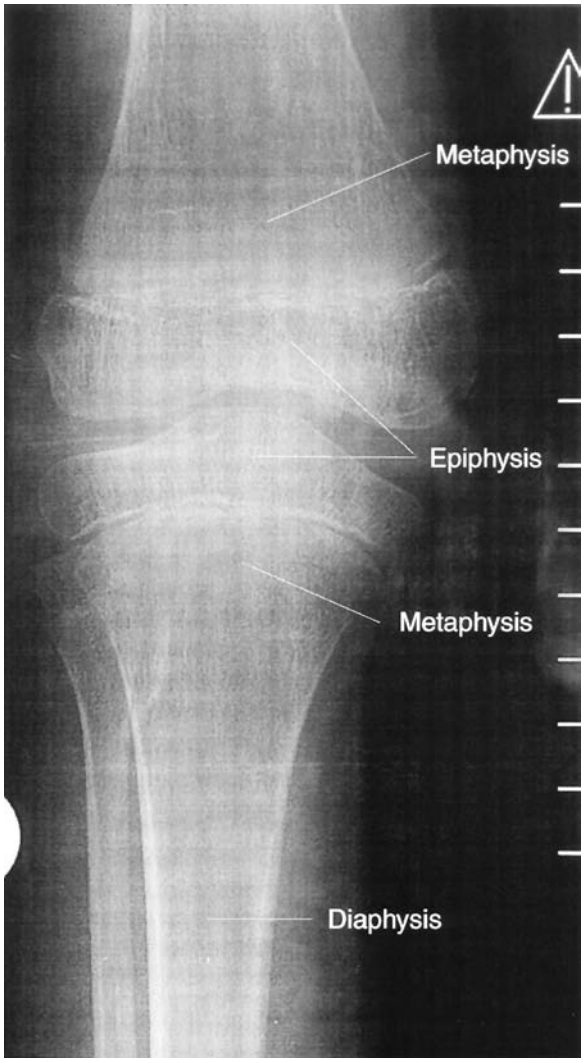

FIGURE 4.
Anteroposterior radiograph of right knee showing epiphysis, metaphysis, and diaphysis.

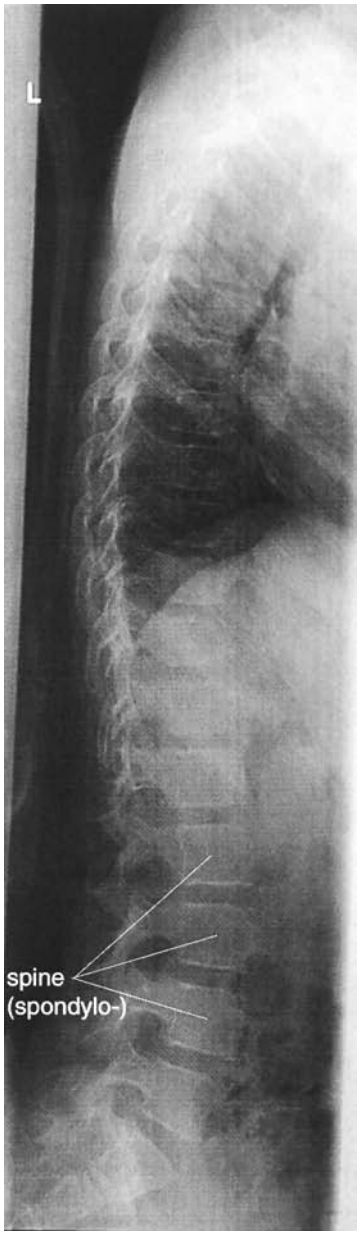

FIGURE 5.
Lateral radiograph of spine showing normal vertebral morphology.

Systematic evaluation of the skeletal survey is made in an attempt to recognize patterns of abnormal skeletal development, growth, and maintenance.[23] Specific note is made of which part of the skeleton is affected (skull, spine, long bones, hands and feet, pelvis, scapulae) and within each bone, the site of the abnormality (Figs 4 and 5). This involves directed assessment of the epiphyses and epiphyseal equivalents (ie, calcaneus, patella), metaphyses, and diaphyses. Attention is paid to the ossification of the skeletal elements with regards to their timing and appearance. This is especially important in conditions with delayed or deficient ossification of the skeleton such as achondrogenesis or atelosteogenesis ("incomplete" ossification). It is important to be aware of the normal time of ossification of each skeletal element,[24] particularly in regard to suspected skeletal dysplasias at termination of pregnancy or in stillborn fetuses. The density of the bone is also important to assess, with both increased and decreased density pointing to specific diagnostic considerations. It is also important to note any secondary arthritic joint disease, as many skeletal dysplasias can predispose to premature arthritis. Some radiographic features are almost pathognomonic of certain entities. Examples are the pelvis and hip findings in achondroplasia, or the hypoplastic scapulae with nonossified thoracic pedicles seen in campomelic dysplasia.[25]

Several skeletal surveys may be required during growth of the skeleton before a specific condition can be diagnosed. There are conditions (ie, spondyloepiphyseal dysplasia congenita and Kniest dysplasia) that can present similarly (clinically and radiographically) in the first year of life that can only be differentiated by careful ongoing follow-up. In these cases, accurate diagnosis is important as these conditions have different natural histories and management despite being caused by mutations in the same gene (type II collagen). In many skeletal dysplasias, diagnosis after epiphyseal fusion is difficult and complicated by nonspecific secondary changes. Chances of making a diagnosis are greatly enhanced by having complete prepubertal skeletal surveys available for analysis. In some cases, even when full clinical and radiographic information is available, no specific diagnosis can be made, and a descriptive label such as "spondylo-epi-metaphyseal dysplasia (unclassified)" is applied.

PRENATAL EVALUATION

The increasing availability, usage, and resolution of prenatal fetal ultrasonography have resulted in increased potential for prenatal diagnosis of these conditions.[26] In most cases, the finding of a short femur length (relative to estimated gestational age) on routine pre-

natal ultrasonography raises the possibility of a skeletal dysplasia. This finding should then lead to a detailed, systematic evaluation of the entire skeleton with regards to establishing a specific diagnosis. Abnormalities in the shape, size, and ossification of the various skeletal elements, as well as specific patterns of findings (ie, bowed femurs in association with hypoplastic scapulae, suggesting campomelic dysplasia), can provide important clues for diagnosis. Increased nuchal translucency measurement in the first trimester of pregnancy can also be associated with various lethal skeletal dysplasias.[27]

Despite the advance in prenatal ultrasonography, diagnosis of a specific skeletal dysplasia remains difficult, with the largest study reporting an accurate prenatal diagnosis by the referring physician in less than one third of cases.[12,26] The International Skeletal Dysplasia Registry has been able to improve on diagnostic accuracy in 81.5% of referred cases,[12] probably reflecting the level of expertise at this center, and its status as a quaternary referral site. This study also reported that the most likely time of diagnosis was between 18 and 20 weeks of gestation (consistent with the timing of the first routine ultrasound examination), with a further cluster in the third trimester as a result of investigation of specific pregnancy complications (eg, polyhydramnios). It is extremely important to try and distinguish between those cases in which a primary bone dysplasia is present and those in which the findings of short limbs are secondary to intrauterine growth retardation or genetic syndromes that can mimic skeletal dysplasia on ultrasound.[28] This can be especially difficult when short limbs are detected in the third trimester. However, in growth-restricted fetuses, there is shortening of the long bones, but their appearance is usually normal. This is not the case in the osteochondrodysplasias because frequently diaphyseal, epiphyseal, and metaphyseal abnormalities can be seen, especially in the third trimester. Detailed surveillance of the appendicular and axial skeleton, in addition to other organ system involvement, may provide clues that will aid in differentiation of growth restriction from skeletal dysplasias, and help delineate a more precise differential diagnosis among the osteochondrodysplasias. Despite the good visualization of the fetal skeleton by ultrasound, 5% of fetuses and stillbirths referred for a suspected skeletal dysplasia to one center were found to have no evidence of either a bone dysplasia or syndrome.[12,26]

It may not be possible to make a specific diagnosis antenatally, but it is important to attempt to find indicators that suggest a high probability of lethality. Such indicators include femur length–to–

abdominal circumference ratio,[29] small bell-shaped thorax, and decreased bone echogenicity.[30] It is paramount that, in all cases where a skeletal dysplasia is suspected antenatally, complete clinical, radiographic and (where appropriate) autopsy examinations are performed to confirm the prenatal suspicion and to make a definitive diagnosis.

CHONDRO-OSSEOUS EVALUATION

A further component of evaluation of the skeletal dysplasias is morphologic studies of chondro-osseous tissue, often done at postmortem.[31,32] In some conditions, histologic examination may confirm a suspected diagnosis by the finding of specific features. An example of this is the striking histologic appearance of the growth plate in the rare and lethal condition, fibrochondrogenesis, which gives the disorder its name.[33] In other conditions, histologic examination may provide important clues to pathogenesis.[34] Some conditions have nonspecific histologic appearances, and this knowledge can be used in ruling out other diagnoses where more specific changes would be expected.

Numerous staining agents can be used to look at chondro-osseous specimens, and they can also be subjected to electron microscope analysis, which may provide clues to pathogenesis. One such finding is dilatation of the chondrocyte rough endoplasmic reticulum (RER). This may indicate defective structure, synthesis, secretion, or processing of an extracellular matrix protein that is subsequently retained in the RER. A specific example of this is pseudoachondroplasia, where dilated loops of RER are observed on electron microscope analysis of growth plate cartilage, reflecting accumulation of mutant cartilage oligomeric matrix protein.[35]

Finally, shared histologic features may point to a similar pathologic basis for apparently unrelated conditions. This was the case in the group of disorders caused by defective sulfate transport in the chondrocyte, where rings of collagen around the resting chondrocytes were observed on histology.[36]

MOLECULAR PATHOGENESIS

Significant recent advances in the field of molecular biology, in conjunction with the results of the human genome project, have facilitated an understanding of the skeletal dysplasias from a molecular viewpoint. The many and varied genes and pathways involved in development, growth, and maintenance of the skeleton are being rapidly elucidated, allowing links to be made between basic molecu-

lar defects and their biochemical and clinical consequences. Further understanding and knowledge about these shared pathways will allow deeper insights into these disorders, better linking genotype to phenotype. It will also facilitate increased availability of diagnostic and prenatal tests to families who choose to use this technology to make reproductive decisions. This understanding may also eventually pave the way for molecular and biochemical approaches to be designed to overcome these basic defects, and reverse or minimize the observed pathology.

We have now reached a stage where a detailed molecular classification can be constructed (Table 1) that brings together disorders that share common etiologic pathways.[2,37,38]

DEFECTS OF STRUCTURAL CARTILAGE PROTEINS

Defects of structural cartilage proteins include collagen types I, II, IX, X, and XI, as well as other extracellular matrix proteins such as COMP (cartilage oligomeric matrix protein). A wide range of phenotypes occurs secondary to mutations in their respective genes. Various mutations in the gene encoding collagen type II, for example, give rise to a "family" of skeletal dysplasias[39] (Table 1) ranging from the lethal (ie, achondrogenesis type 2) to the relatively mild (ie, Stickler syndrome).

DEFECTS OF CARTILAGE METABOLIC PATHWAYS

Defects of cartilage metabolic pathways comprise defects of enzymes, ion channels, and transporters essential for cartilage metabolism and homeostasis (Table 1). An example of this group is the spectrum of sulfate transporter skeletal dysplasias. These conditions (which range in severity from lethal in utero to a mild epiphyseal dysplasia with normal height) are caused by varying degrees of impaired sulfate transport into chondrocytes.[40] Sulfate incorporation into cartilage cells is crucial for usurpation of extracellular matrix molecules, and impairment of this process results in various degrees of abnormal chondrogenesis, proportional to the degree of transporter compromise.[40]

DEFECTS IN LOCAL REGULATION OF CARTILAGE GROWTH

Defects in local regulation of cartilage growth include disorders caused by abnormalities in hormones, growth factors, and their various receptors that affect cartilage growth and proliferation via paracrine, autocrine, or endocrine signaling systems. Prime examples of this group of disorders are the spectrum of disorders caused by mutations in the fibroblast growth factor receptor genes (*FGFR1*, *2,* and

3) that range from isolated craniosynostosis to achondroplasia, the single most common skeletal dysplasia[41] (Table 1).

DEFECTS IN TRANSCRIPTION FACTORS

Defects in a wide array of transcription factors[42] give rise to a variety of skeletal phenotypes ranging from generalized, severe skeletal dysplasias to more localized "dysostoses." In addition, homozygous and heterozygous mutations in these "master" genes can cause a variety of phenotypes, as evidenced by the group of conditions[43] (Table 1) caused by mutations in the short-stature homeobox gene (*SHOX*).

DEFECTS IN TUMOR SUPPRESSOR GENES

Abnormalities in tumor suppressor genes (Table 1) give rise to the multiple hereditary exostoses syndromes via disordered regulation of cartilage growth with the potential for malignant change.[44]

MANAGEMENT OF THE SKELETAL DYSPLASIAS

The optimal management of this diverse group of conditions requires consideration of their medical, psychosocial, and architectural consequences. This is often best achieved by centers that are able to offer families a multidisciplinary approach, working in conjunction with relevant pediatric and adult physicians. Achondroplasia, the most common of the skeletal dysplasias (estimated incidence, 1 per 20,000 live births), serves as a prime example to illustrate these key principles.

Most persons with achondroplasia are of normal intelligence, have a normal life span, and lead independent and productive lives. However, they face many potential medical, psychosocial, and architectural challenges secondary to their abnormal skeletal development and subsequent disproportionate short stature.[45] The mean final adult height in achondroplasia is 130 cm for men and 125 cm for women, and specific growth charts have been developed to document and track linear growth, head circumference, and weight in these patients.[46,47] Human growth hormone and other drug therapies have not been effective in significantly increasing final adult stature in achondroplasia, although short-term gains have been reported.[48] Recently, surgical limb-lengthening procedures have been used successfully to increase leg length by up to 12 inches, but opinion regarding the standard use of this procedure in achondroplasia remains divided.[49]

There are many potential medical problems that patients with achondroplasia may experience during their life. In early infancy, the most potentially serious of these is compression of the cervico-

medullary spinal cord secondary to a narrow foramen magnum, cervical spinal canal, or both. This complication may be manifest clinically by symptoms and signs of high cervical myelopathy, central apnea or profound hypotonia,[C] and motor delay and may, in some instances, require decompressive neurosurgery.[50] Other potential complications in infancy include significant nasal obstruction that may lead to sleep apnea in a minority (5%), development of a thoracolumbar kyphosis, which usually resolves upon weight bearing, and hydrocephalus in a small proportion (1%) during the first 2 years of life, which may require shunting.[50]

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From early childhood, and as the child begins to walk, several orthopedic manifestations may evolve including progressive bowing of the legs caused by fibular overgrowth, development of lumbar lordosis, and hip flexion contracture. Obesity can be a problem for many persons with achondroplasia,[51] with its primary adverse health outcomes as well as its secondary effects, including increased orthopedic complications and decreased self-esteem. Recurrent ear infections with ensuing chronic serous otitis media are common complications at this time and may lead to conductive hearing loss with consequent delayed speech and language development.

The older child with achondroplasia commonly develops dental malocclusion secondary to a disproportionate cranial base and midface, with subsequent crowding of teeth. The main potential medical complication of the adult with achondroplasia is lumbar spinal canal stenosis, with impingement on the spinal cord roots. This complication may be manifested by lower limb pain and parasthesias, bladder or bowel dysfunction, and neurologic signs and may require decompressive surgery.[51]

Throughout their lives, persons with achondroplasia and their families may experience a variety of psychosocial challenges.[52] These can be addressed by specialized medical and social support of the individual and family, appropriate anticipatory guidance, and by interaction with patient support and advocacy groups such as the Little People of America. Guidelines for the health supervision of children with achondroplasia have been formulated[53] and can be used as a template for surveillance.

As many generalized skeletal dysplasias result in short stature, it is important to seek input from allied health care specialists who can work with patients and their families to modify home and work appliances as necessary. This aims to enhance the autonomy of these individuals, allowing them the best opportunity to reach their potential. It is important that education of health care workers and the wider community (ie, schools and workplaces) regarding these con-

ditions is undertaken so that persons with these conditions can go about their lives without fear of the discrimination or "stigma" that has been historically attached to these "dwarfing" conditions.

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