Heritable Diseases of Connective Tissue
DEBORAH KRAKOW

SKELETAL DYSPLASIAS

The skeletal dysplasias, or osteochondrodysplasias, are defined as disorders that are associated with a generalized abnormality in the skeleton. Although each skeletal dysplasia is relatively rare, collectively, the birth incidence of these disorders is almost 1 in 5000. These disorders range in severity from “precocious” arthropathy to perinatal lethality owing to pulmonary insufficiency. Individuals with these disorders can have significant orthopedic, neurologic, and psychological complications. Many of these individuals seek medical attention for orthopedic complaints owing to ongoing pain, arthritic complaints in large joints, and back pain primarily caused by ongoing abnormalities in bone and cartilage frequently leading to spinal stenosis.

Embryology

The human skeleton (from the Greek, skeletos, “dried up”) is a complex organ consisting of 206 bones (126 appendicular bones, 74 axial bones, and 6 ossicles). The skeleton including tendons, ligaments, and muscles in addition to cartilage and bone has multiple embryonic origins and serves many key functions throughout life such as linear growth, mechanical support for movement, a blood and mineral reservoir, and protection of vital organs.

The patterning and architecture of the skeleton occurs during fetal development (see Chapter 4). During that period, the number, size, and shape of the future skeletal elements are determined, a process that is under complex genetic control. Uncondensed mesenchyme undergoes cellular condensations (cartilage anlagen) at the sites of future bones, and this occurs via two mechanisms. In the process of endochondral ossification, mesenchyme first differentiates into a cartilage model (anlagen), and then the center of the anlagen degrades, mineralizes, and is removed by osteoclast-like cells. This process spreads up and down the bones and allows for vascular invasion and influx of osteoprogenitor cells. The periosteum in the midshaft region of the bone produces osteoblasts, which synthesize the cortex; this is known as the primary ossification center.

At the ends of the cartilage anlagen, 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 area is referred to as a cartilage growth plate or epiphysis. Four chondrocyte cell types exist in the growth plate: reserve, resting, proliferative, and hypertrophic. These growth plate chondrocytes undergo a tightly regulated program of proliferation, hypertrophy, degradation, and replacement by bone (primary spongiosa). This is the major mechanism of skeletogenesis and is the...
mechanism by which bones increase in length, and the articular surfaces increase in diameter. In contrast, the flat bones of the cranial vault and part of the clavicles and pubes form by intramembranous ossification, whereby fibrous tissue, derived from mesenchymal cells, differentiates directly into osteoblasts, which directly lay down bone. These processes are under specific and direct genetic control, and abnormalities in the genes that encode these pathways frequently lead to skeletal dysplasias.6,9

**Cartilage Structure**

Collagen accounts for two-thirds of the adult weight of adult articular cartilage and provides significant strength and structure to the tissue (see Chapter 3). Collagens are a family of proteins that consist of single molecules (monomers) that combine into three polypeptide chains to form a triple helix structure. In the triple helix, every third amino acid is a glycine residue and the general chain structure is denoted as Gly-X-Y, where X and Y are commonly proline and hydroxyproline. The collagen helix can be composed of identical chains (homotrimeric), as in type II collagen, or can consist of different collagen chains (heterotrimeric), as seen in collagen type XI.10

Collagens are widely distributed throughout the body, and 33 collagen gene products are expressed in a tissue-specific manner, leading to 19 triple helical collagens. Collagens are classified further by the structures they form in the extracellular matrix. The most abundant collagens are the fibrillar types (I, II, III, V, and XI), and their extensive cross-linking provides mechanical strength that is necessary for high stress tissue such as cartilage, bone, and skin.11 Another collagen species is the fibril-associated collagens with interrupted triple helices, which include collagen types IX, XII, XIV, and XVI. These collagens interact with fibrillar collagens and other extracellular molecules including aggrecan, cartilage oligomeric matrix protein, and other sulfated proteoglycans.11 Collagen types VIII and X are non-fibrillar, short-chain collagens, and type X collagen is the most abundant extracellular matrix molecule expressed by hypertrophic chondrocytes during endochondral ossification.12 The major collagens of articular cartilage are fibrillar collagen types II, IX, X, and XI. In developing cartilage, the core fibrillar network is a cross-linked copolymer of collagens II, IX, and XI.13 Mutations in genes that encode these collagens and proteins involved in their processing result in various skeletal dysplasias and highlight the importance of these molecules in skeletal development.

**Classification and Nomenclature**

As mentioned earlier, in the 1970s, there was recognition of the genetic and clinical heterogeneity of heritable disorders of connective tissue and a new awareness of the complexity of these disorders. As a result, there have been multiple attempts to classify these disorders in a manner that clinicians and scientists could use effectively to diagnose and determine their pathogenicity (International Nomenclature of Constitutional Diseases of Bone, 1970, 1977, 1983, 1992, 2001, 2005, 2010). The initial categories were purely descriptive and clinically based. With the more recent explosion in determining the genetic basis of these diseases, the classification has evolved into one that combines the older clinical one (including the eponyms and Greek terms) and blends these disorders into families that share a molecular basis or pathway. The most recent updated classification can be found at www.isds.ch. Some of the chondrodysplasia families are listed in Table 105-1.

The most widely used method for differentiating the skeletal disorders has been through the detection of skeletal radiographic abnormalities. Radiographic classifications are based on the different parts of the long bones that are abnormal (epiphyses, metaphyses, and diaphyses) (Figure 105-1). These epiphyseal, metaphyseal, and diaphyseal disorders can be differentiated further depending on whether or not the spine is involved (spondyloepiphyseal, spondylo-metaphyseal, or spondyloepimetaphyseal dysplasias). The classes of these disorders can be differentiated further into distinct disorders on the basis of other clinical and radiographic findings.

**Clinical Evaluation and Features**

The skeletal dysplasias are generalized disorders of the skeleton and usually result in disproportionate short stature. Affected individuals usually present because they are disproportionately short. This finding needs to be documented on the appropriate growth curves for gender and ethnicity if possible. As a generalization, most individuals with disproportionate short stature have skeletal dysplasias, and individuals with proportionate short stature have endocrine, nutritional, or prenatal-onset growth deficiency or other disorders. Exceptions to the rule include congenital hypothyroidism, which is associated with disproportionate short stature, and disorders such as osteogenesis imperfecta (OI) and hypophosphatasia can be associated with normal body proportions.

A disproportionate body habitus may not be immediately visible on physical examination. Anthropometric dimensions such as upper-to-lower segment (U/L) ratio, sitting height, and arm span must be measured when considering the possibility of a skeletal dysplasia and should be measured in centimeters. Sitting height is an accurate measurement...
Table 105-1  Classification of the Chondrodysplasias

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Inheritance</th>
<th>Gene</th>
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<tbody>
<tr>
<td><strong>Achondroplasia Group</strong></td>
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<tr>
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<td>(Toledo type)</td>
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<td>SHOX</td>
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<td>SHOX</td>
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<tr>
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<td>Duplicated in the Hox cluster</td>
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of head and trunk length, but it requires special equipment for precise measurements. U/L ratios are easy to obtain and provide an accurate measurement of proportion. The lower segment is measured from the symphysis pubis to the floor at the inside of the heel. The upper segment is measured by subtracting the lower segment measurement from the total height. McKusick\(^{14}\) has published standard U/L segment ratios for whites and African-Americans across ages. An average-height white child 8 to 10 years old has a U/L segment ratio of approximately 1 and as an adult has a U/L segment ratio of 0.95. Individuals presenting with disproportionate short stature have altered U/L segment ratios depending on whether they have short limbs, short trunk, or both. An individual with short limbs and normal trunk has an increased U/L segment ratio, and an individual with normal limbs but short trunk has a diminished U/L segment ratio (Figure 105-2). Another means of determining if there is disproportion is based on arm span measurements, which are close to total height in an average-proportioned individual. A short-limbed individual has an arm span considerably shorter than the height.

As in any disorder that has a genetic basis, it is crucial to obtain an accurate family history. This should include any history of previously affected children or parental consanguinity. The skeletal dysplasias are genetically heterogeneous and can be inherited as autosomal dominant, autosomal recessive, X-linked recessive, and X-linked dominant disorders, and rarer genetic mechanisms of disease including germline mosaicism, uniparental disomy, and chromosomal rearrangements have been seen.\(^{15,18}\) For many patients and families, accurate diagnosis and recurrence risk can have a significant impact on their reproductive decisions. Another consideration for patients with short stature is that there is increased nonrandom mating, which leads to reproductive outcomes that have been previously unknown.\(^{19,20}\) Homozygous achondroplasia is lethal, and many newborns who inherit two dominant mutations (compound heterozygotes) die early with severe abnormalities of the skeleton.\(^{21}\) It is also important to obtain an accurate history relative to the onset of short stature and whether it developed immediately in the postnatal period or was noticed at age 2 or 3. Of the 450 skeletal dysplasias, approximately 100 of them have onset in the prenatal period, but many affected individuals do not develop disproportionate short stature and joint discomfort until childhood.\(^{22,23}\)

A detailed physical examination may reveal a diagnosis or help differentiate the most likely group of possible diagnoses. It is crucial when disproportion and short stature have been established and the limbs are involved to determine which segment is involved: upper segment (rhizomelic—humerus and femur); middle segment (mesomelic—radius, ulna, tibia, and fibula); and distal segment (acromelic—hands and feet). Numerous head and facial dysmorphisms are seen in the skeletal disorders. Affected individuals frequently have disproportionately large heads. Frontal bossing and flattened nasal bridge are characteristic of achondroplasia, one of the most common skeletal dysplasias.\(^{24}\) Cleft palate and micrognathia are commonly found in the type II collagen abnormalities, abnormally flattened midface with

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**Table 105-1  Classification of the Chondrodysplasias—cont’d**

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Dysplasia with Prominent Membranous Bone Involvement</th>
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<td></td>
<td>Clearance with prominent membranous bone involvement</td>
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<td>Fibrillin 1</td>
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AD, autosomal dominant; AR, autosomal recessive; CATSHL, camptodactyly, tall stature, and hearing loss syndrome; OSMED, otospondylometaepiphyseal dysplasia; SADDAN, severe achondroplasia with developmental delay and acanthosis nigricans; TRPV4, transient receptor potential vanilloid 4; XLR, X-linked recessive; XLD, X-linked dominant.

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**Figure 105-2**  Upper segment length/lower segment length (U/L) in 8- to 10-year-old individuals with short limb and short trunk dwarfism. The child on the left has short limbs and an increased U/L ratio; the child on the right has a short trunk and reduced U/L ratio.
a turned-up nose is frequently found in the chondrodysplasia punctata disorders, and abnormal swollen pinnae are seen in diastrophic dysplasia. Individuals with skeletal dysplasias should be screened for ophthalmologic and hearing abnormalities because many of these disorders are associated with eye abnormalities and hearing loss.

Further evaluation of the hands and feet can lead to further differentiation of these disorders. Postaxial polydactyly is characteristically found in chondroectodermal dysplasia and the short-rib polydactyly disorders (see Table 105-1). Short, hypermobile, radially displaced thumbs are seen in diastrophic dysplasia. Nails can be abnormally hypoplastic in chondroectodermal dysplasia and short and broad in cartilage hair hypoplasia. Clubfeet may be seen in many disorders including Kniest dysplasia, spondyloepiphysial dysplasia congenita, Larsen syndrome, varying forms of osteogenesis imperfecta, and diastrophic dysplasia. Bone fractures occur most commonly in two types of disorders—those that result from undermineralized bone (OI, hypophosphatasia, achondrogenesis 1A), or those that result from overmineralized bone (osteopetrosis syndromes and dysostoeosclerosis).

Organ systems other than the skeleton can be involved, although rarely. Congenital cardiac defects are seen in chondroectodermal dysplasia (atrial septal defects), the short-rib polydactyly disorders (complex outlet defects including isolated ventricular septal defects), and Larsen syndrome (ventricular septal defects). Gastrointestinal anomalies are rare among the skeletal disorders, but congenital megacolon can be seen in cartilage hair hypoplasia, malabsorption syndrome in Schwachmann-Diamond syndrome, and omphaloceles in otopalatodigital syndrome and atelosteogenesis I.

Diagnosis and Testing

After obtaining a thorough family history and physical examination, the next step is to obtain a full set of skeletal radiographs. A full series of skeletal views includes anterior, lateral, and Towne views of the skull; anterior and lateral views of the entire spine; and anteroposterior views of the pelvis and extremities, with separate views of the hands and feet, especially after the newborn period. Most of the important clues to diagnosis are in skeletal radiographs that are obtained before puberty. When the epiphyses have fused to the metaphyses, determining the precise diagnosis can be extremely challenging. If an adult is evaluated, all attempts should be made to obtain any available childhood radiographs. Many subtle clues in these skeletal radiographs can lead to precise diagnosis. Demonstrating punctate calcifications in the areas of the epiphyses in the chondrodysplasia punctata disorders, multiple ossification centers of the calcaneus in more than 20 disorders, and the type of hand shortening can aid in differentiating many disorders.

After obtaining radiographs, close attention should be paid to the specific parts of the skeleton (spine, limbs, pelvis, skull) involved and to the location of the lesions (epiphyses, metaphyses, and vertebrae) (Figure 105-3). As mentioned earlier, these radiographic abnormalities can change with age, and if available, radiographs across a few years or decades aid in diagnosis. Fractures can be seen in OI (all types) (Figure 105-4; see Table 105-1) and severe hypophosphatasia. In older individuals, fractures may be seen in disorders associated with increased mineralization such as the osteopetrosis syndromes and dysostoeosclerosis. When a thorough evaluation of the radiographs reveals abnormalities, but a diagnosis still cannot be made, resources are available. The International Skeletal Dysplasia Registry and European Skeletal Dysplasia Network are available to provide diagnosis for these rare disorders.

Morphologic studies of chondro-osseous tissue have revealed specific abnormalities in many of the skeletal dysplasias. In these disorders, histologic evaluation of chondro-osseous morphology can aid in making an accurate diagnosis, and absence of histopathologic alterations can rule out diagnoses. These studies need to be done on cartilage growth plate, and although commonly performed on perinatal lethal skeletal disorders at autopsy, obtaining

![Figure 105-3](image_url) Radiographs showing abnormalities in the chondrodysplasias, specifically pseudoachondroplasia. A, Irregular metaphyses and small epiphyses. B, Small, rounded vertebrae with anterior beaking.
growth plate histology on individuals with nonlethal disorders is difficult. If affected individuals (children) are undergoing surgery, an iliac crest biopsy specimen can be evaluated.

Histomorphology studies done on these disorders have led to important insights on the pathogenesis of these disorders. On morphologic grounds, the chondro dysplasias can be broadly classified into disorders (1) that have a qualitative abnormality in endochondral ossification, (2) that have abnormalities in cellular morphology, (3) that have abnormalities in matrix morphology, and (4) in which the abnormality is primarily localized to the area of chondro-osseous transformation. In thanatophoric dysplasia, there is a defect in endochondral ossification with a short, almost hypertrophic zone; shortened proliferative zone; and overgrowth of the periosteum. In pseudoachondroplasia, there is a distinct lamellar pattern (alternating electron-dense and electron-lucent lamellae) in the rough endoplasmic reticulum of chondrocytes (Figure 105-5) and a grossly abnormal matrix in diastrophic dysplasia, which leads to a characteristic ring around the chondrocytes. All of these findings are characteristic and diagnostic for these disorders and illustrate how morphology studies can have an integral part in the investigation of these disorders.

There has been significant progress in gene identification in these disorders, which has impact for affected individuals. As illustrated in Table 105-1, for disorders in which the gene is identified, molecular diagnostic testing is potentially available. Molecular diagnosis can be used to confirm a clinical and radiographic diagnosis, predict carrier status in families at risk for a recessive disorder, and, for some individuals, allow for prenatal diagnosis of at-risk fetuses. Because these are rare disorders, commercial testing is not always readily available; however, GeneTests (www.genetests.org) is a publically funded medical genetics website developed for physicians that provides information on diseases and available genetic testing.

**Management and Treatment**

The optimal management of this diverse set of disorders requires an understanding of the medical, skeletal, and psychosocial consequences. This is often best accomplished by centers that have a multidisciplinary approach, which includes adult and pediatric physicians, orthopedists, rheumatologists, otolaryngologists, neurologists, neurosurgeons, and ophthalmologists who are committed to the care of these patients.

Most medical complications in these disorders result from orthopedic complications, and they vary depending on the specific disorder. In disorders associated with significant odontoid hypoplasia such as Morquio disease, type II collagenopathies, metatropic dysplasia, and Larsen syndrome, flexion-extension films should be monitored at regular intervals to assess for C1-C2 subluxation. Many experts in the field now believe that all individuals with skeletal dysplasias should have evaluation of their cervical spine, regardless of diagnosis. If there is evidence for subluxation, surgery for C1-C2 fixation is indicated. Genu varum—lateral curvature of the lower extremity—is common in many skeletal disorders caused by overgrowth of the fibula; this causes knee or ankle pain in many individuals, especially children, and correction by osteotomy should be
considered. Children and adults with skeletal dysplasias should have regular eye and hearing examinations because they are at increased risk for myopia, retinal degeneration, glaucoma, and hearing loss depending on the disorder. 

Frequently, patients with these disorders have significant joint pain and in some cases joint limitations. Because most of these disorders result from mutations in genes crucial to cartilage function, the cartilage at the joint surfaces may not provide adequate support and cushioning function. Many of these patients seek attention for joint pain. Evaluation should include radiographs and magnetic resonance imaging (MRI), when appropriate, to determine the etiology of the pain. In some disorders such as the type II collagenopathies, pseudoachondroplasia, multiple epiphyseal dysplasia, and cartilage hair hypoplasia, by adulthood, so little cartilage remains at the knee or hips that joint replacement is indicated for pain relief. Lastly, overweight in adults with short stature is an ongoing issue and contributes to inactivity, loss of function, adult-onset diabetes, hypertension, and coronary disease.29

**Achondroplasia**

Achondroplasia is the most common of the nonlethal skeletal dysplasias (approximately 1 in 20,000) and serves as an example on how to approach these disorders. Most affected individuals are of normal intelligence, have a normal life span, and lead independent and productive lives. The mean final height in achondroplasia is 130 cm for men and 125 cm for women; specific growth charts have been developed to document and track linear growth, head circumference, and weight in these individuals.30-32

In early infancy, there is potentially serious compression of the cervico-medullary spinal cord secondary to a narrow foramen magnum, cervical canal, or both. Clinically, these infants have central apnea, sleep apnea, profound hypotonia, motor delay, emesis while forward positioned in car seats, or excessive sweating. MRI with flow studies is necessary to document the obstruction; if present, obstruction requires decompressive surgery.33 Other complications include nasal obstruction, venous distention, thoracolumbar kyphosis, and hydrocephalus in a few individuals.34

From early childhood, and as children begin to walk around 22 to 24 months, they develop several orthopedic manifestations, which include progressive bowing of the legs owing to fibular overgrowth, lumbar lordosis, and hip flexion contractures. Recurrent ear infections can lead to chronic serous otitis media and deafness. Tympanic membrane tube placement is indicated in many of these patients. Craniofacial abnormalities lead to dental malocclusion, and appropriate treatment is necessary. In adults, the main potential medical complication is impingement of the spinal root canals. This complication can be manifested by lower limb paresthesias, claudication, clonus, or bladder or bowel dysfunction. It is crucial that these complaints are addressed because without appropriate decompression surgery, spinal cord paralysis may result.35

Growth hormone has not been effective in increasing height in this disorder.36 Surgical limb lengthening has been employed successfully to increase limb length by 12 inches,37 but this technique needs to be done during the teen years and is performed over a 2-year period and is associated with complications. Recent advances in the molecular understanding underlying achondroplasia have identified molecular targets to potentially treat the disorder, thus improving height and orthopedic complications. Achondroplasia results from heterozygosity for mutations in the gene that encodes fibroblast growth factor receptor 3 (FGFR3). The mutation causes constitutive activation of the receptor leading to increased MAPK signaling with elevated levels of ERK1/2 phosphorylation. Molecules targeted to the tyrosine kinase domain of the receptor and those that diminish ERK signaling have shown efficacy in tissue and animal models. Throughout their lives, individuals with achondroplasia and other skeletal dysplasias and their families experience various psychosocial challenges.38 These challenges can be addressed by specialized medical and social support systems. Interactions with advocacy groups such as Little People of America (www.lponline.org) can provide emotional support and medical information.

### Biochemical and Molecular Abnormalities

Similarities in clinical and radiographic findings and histomorphology have placed bone dysplasia into families.39-41 These families share common pathophysiologic or pathway mechanisms. In recent years, there has been an explosion in understanding of the basic biology of these disorders. This explosion has resulted from the successful human genome project, which improved various methodologies including candidate gene approach, linkage analysis, positional cloning, human/mouse synteny, array comparative genomic hybridization, and massive parallel sequencing (whole exome or whole genome analyses) allowing for identification of the disease genes (see Table 105-1). With gene discovery in the vast number of these osteochondrodysplasias, these genes can be placed into several categories designed to understand their pathogenesis: (1) defects in extracellular proteins; (2) defects in metabolic pathways (enzymes, ion channels, and transporters); (3) defects in folding and degradation of macromolecules; (4) defects in hormones and signal transduction; (5) defects in nuclear proteins; (6) defects in oncogenes and tumor-suppressor genes; (7) defects in RNA and deoxyribonucleic acid (DNA) processing molecules; (8) defects in intracellular structural and organelle proteins; (9) microRNAs; and (10) genes of unknown function. There are still skeletal dysplasias for which the gene and mechanism of disease are unknown. Following are descriptions of some of the molecular mechanisms involved in the skeletal dysplasias.

### DEFECTS IN EXTRACELLULAR STRUCTURAL PROTEINS

#### Type II Collagen and Type XI Collagen

Because type II collagen was found primarily in cartilage, the nucleus pulposus, and the vitreous of the eye, it was hypothesized that skeletal disorders with significant spine and eye abnormalities would result from defects in type II collagen. Type II collagen defects have been identified in a spectrum of disorders ranging from lethal to mild arthropathy, which include achondrogenesis II, hypochondrogenesis, spondyloepiphysyeal dysplasia congenita,
spondyloepimetaphyseal dysplasia, Strudwick type, Kniest dysplasia, Stickler syndrome, spondyloperipheral dysplasia, and "precocious" familial arthropathy. These disorders are referred to as type II collagenopathies, and they all result from heterozygosity for mutations in COL2A1.\textsuperscript{52,47} Biochemical analysis of cartilage derived from these individuals shows electrophoretically detectable abnormal type II collagen. Type I collagen is not normally present in cartilage, but in the presence of abnormal type II collagen there is increased type I collagen in the growth plate.

Mutations that result in a substitution for a triple helical glycine residue seem to be the most common type of mutation.\textsuperscript{44} There are some correlations between the location of the mutation and the disease phenotype. In spondyloepiphyseal dysplasia, the glycine substitutions are scattered throughout the molecule; however, in Kniest dysplasia, the mutations are in the more amino-terminal end of the molecule.\textsuperscript{44,46} Stickler syndrome, a disorder of mild short stature, arthropathy, and high-grade myopia (see Table 105-1), is genetically heterogeneous and results from mutations in COL2A1 and COL11A1, and nonocular forms result from mutations in COL11A2.\textsuperscript{47,48} In Stickler syndrome, the COL2A1 and COL11A1 mutations tend to be nonsense mutations resulting in premature translation stop codons; however, patients with COL11A1 mutations tend to have a more severe eye phenotype and hearing loss than patients with COL2A1 mutations.

Individuals heterozygous for various COL11A2 mutations\textsuperscript{49} have a nonocular form of Stickler syndrome, consistent with the absent expression of COL11A1 in the vitreous humor. Oto-spondylo-epiphyseal dysplasia is a rare autosomal recessive disorder caused by loss of function mutations in COL11A2.\textsuperscript{50} This disorder has radiographic similarities to Kniest dysplasia but is associated with profound sensorineural hearing loss and lack of ocular involvement. Recent discoveries have extended the spectrum of disease for type XI collagen. Autosomal recessive fibrochondrogenesis, a severe skeletal dysplasia, highly associated with lethality, results from mutations in the two genes that encode type XI, COL11A1 and COL11A2.\textsuperscript{51,52} Type II and XI collagens form a heterotypic fibril in the cartilage matrix and not surprisingly, there is significant clinical overlap in the disorders due to mutation in the genes that encode these collagens.

**Cartilage Oligomeric Matrix Protein**

Heterozygosity for mutations in cartilage oligomeric matrix protein leads to pseudoachondroplasia and multiple epiphyseal dysplasia.\textsuperscript{53} Cartilage oligomeric matrix protein is a member of the thrombospondin family of proteins and consists of an epidermal growth factor domain and calcium binding, calmodulin domain.\textsuperscript{54} In pseudoachondroplasia and multiple epiphyseal dysplasia, disease-producing mutations occur in the calmodulin domain, with a few in the globular carboxy-terminal domain (Figure 105-6). As opposed to pseudoachondroplasia, multiple epiphyseal dysplasia results from heterozygosity for mutations in numerous genes (COL9A1, COL9A2, COL9A3, and MATRILIN3), and there is a recessive form due to mutations in the DTDST gene. Both these disorders are associated with significant early destruction of cartilage with many affected individuals undergoing hip and knee replacements at an early age.

**Defects in Metabolic Pathways**

Defects in metabolic pathways comprise defects in enzymes, ion channels, and transporters essential for cartilage metabolism and homeostasis. An example is the diastrophic dysplasia group (see Table 105-1), a spectrum of disorders (lethal to mild short stature) resulting from mutations in the DTDST (SLC26A2) gene. These disorders result from a varying defect in the degree of sulfate uptake or transport into chondrocytes.\textsuperscript{55} Lack of adequate intracellular sulfate affects the normal post-translational modification of proteoglycans and leads to abnormal chondrogenesis that is proportional to the degree of transporter compromise.\textsuperscript{50} Affected individuals suffer from severe degenerative joint disease.

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**Figure 105-6** Diagram of the cartilage oligomeric matrix protein delineating the domains—NH\textsubscript{2}, amino terminus, epidermal growth factor-like (EGF-like), calmodulin-like, carboxy-terminus (COOH), pseudoachondroplasia (PSACH), and multiple epiphyseal dysplasia (MED). Amino acid substitutions are listed below the molecule.
Defects in Intracellular Structural Proteins

Intracellular proteins are ubiquitously expressed proteins; the finding that mutations in the genes encoding filamin A and filamin B produced primarily skeletal disorders was surprising.56-58 The filamins are cytoskeleton proteins involved in multicellular processes including providing structure to the cell, facilitating signal transduction and transport of small solutes, allowing communication between the intracellular and extracellular environment, and participating in cell division and motility. Defects in these genes have a profound effect on the skeleton ranging from absence of bone formation to significant joint dislocations. The mechanisms by which these mutations produce disease are unclear, though alterations in the cellular and organelle functions are beginning to be elucidated.59

Defects in Membrane Channels

Calcium homeostasis is critical for cartilage and bone.59,60 TRPV4, or transient receptor potential cation channel subfamily V member 4, is a cation channel that mediates calcium influx in response to numerous stimuli. The importance of this channel has been demonstrated because it produces a vast spectrum of autosomal dominant skeletal disorders including lethal metatropic dysplasia, non-lethal metatropic dysplasia, spondyloepiphyseal dysplasia, Koslowski type, and brachyolmia.61,62 In addition, heterozygosity for mutations in TRPV4 also causes neuromuscular diseases without notable boney manifestation that include hereditary motor and sensory neuropathy type IIC, congenital spinal muscular atrophy, and scapuloperoneal spinal muscular atrophy.64-66 The mechanism by which these mutations scattered throughout the molecule produce such divergent phenotypes is unclear but supports some common pathway in tissues of mesenchymal origin.

Summary

Although these osteochondrodysplasias are rare disorders, affected individuals have significant skeletal complications throughout their lives, first owing to patterning defects, then effects on linear growth, and finally loss of normal structural cartilage as a cushion later in life. The explosion in delineating the molecular defects has shown the complexity of cartilage as a tissue and the large number of cellular processes necessary for a normal skeleton.

OSTEOGENESIS IMPERFECTA

OI is a heritable disorder of bone and was one of the first disorders hypothesized to be a defect in collagen by McKusick.1 Although an osteochondrodysplasia, OI is discussed separately from the chondrodysplasias delineated previously. OI is a generalized disorder of connective tissue that predominantly affects the skeletal system61 and affects numerous individuals (estimates at about 1 in 20,000 individuals).

Initially, there were four types of recognized OI in the clinical classification of Silcence.68 There are now seven well-recognized forms of OI, and through recent gene discoveries it is apparent that a clinical classification system is no longer useful. Because there is enormous clinical variability in these types, the subtypes are discussed separately using historical classifications, but many experts advocate using the terms mild, moderate, and severe (Table 105-2). These disorders all share the same phenotypic finding of hypomineralization of the skeleton.

Mild Osteogenesis Imperfecta (Type I)

Affected individuals with OI type I disease have mild disease in terms of clinical course, the extent of skeletal deformity, and the radiologic appearance of the skeleton (see Figure 105-4A and Table 105-2). They also account for most individuals with OI. Individuals are usually short for their age or their unaffected family members. Many of these individuals experience numerous fractures, especially in childhood; children with OI type I may have 20 fractures by the age of 5.

The disorder is autosomal dominant, and in many cases the individual is the first affected in the family. There is mild facial dysmorphism in OI type I with a mild triangular facial shape. The blue sclerae become gray-to-pale blue in adulthood. Arcus senilis not related to lipid abnormalities may occur in some patients. Other reported ocular defects include scleromalacia, keratoconus, and retinal detachment.69 Teeth frequently show dentinogenesis imperfecta owing to the effects of mutation on the tooth dentin. The deciduous and permanent teeth have an opalescent and translucent appearance, which tends to darken with age. The enamel is normal, but the dentin is dysplastic; chipping of enamel occurs, and the teeth are subjected to erosion and breakage. Teeth of affected individuals appear discolored or gray. This finding varies in the disorder but does co-segregate in families with OI. During the second and third decades of life, a characteristic high-frequency sensorineural or mixed hearing loss can be detected.70 The incidence of mitral valve prolapse is not increased in these patients compared with the population at large, but individual kindreds with increased diameter of the aortic root or patients with aortic regurgitation have been reported.71 Many patients complain of easy bruising, and this may result from the effects of mutation on skin and the vessels below.

Mildly affected patients may not have fractures at birth, although occasionally a fracture of a clavicle or extremity occurs during delivery. Radiographically, affected newborns have wormian bones seen on lateral views of the skull, with significant osteopenia seen through the skeleton, especially the spine. Often, the frequency of fracture depends on the child’s activity, the need for immobilization after lower extremity fractures, and the attitude of the family toward independent activity. Generally, these patients may experience 5 to 15 major fractures before puberty and several minor traumatic fractures of the digits or the small bones of the feet. Characteristically, the fracture rate declines dramatically after puberty, only to increase during later life. Mild scoliosis approximating 20 degrees is common. Osteopenia is observed in vertebral bodies and the peripheral skeleton and progresses with age. In mild OI, the long bones usually heal with no significant deformity. Compared with more severe phenotypes, children with mild OI only infrequently require the insertion of intramedullary rods and almost never experience nonunion at a fracture site.
Table 105-2  Classification and Molecular Basis of Osteogenesis Imperfecta

<table>
<thead>
<tr>
<th>OI</th>
<th>Clinical Features</th>
<th>Inheritance</th>
<th>Biochemical Abnormality</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (type I)</td>
<td>Normal stature, little or no deformity, blue sclerae, hearing loss, dentinogenesis imperfecta</td>
<td>AD (new mutations are common)</td>
<td>50% reduction in type I collagen synthesis</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Lethal (type II)</td>
<td>Lethal; minimal calvarial mineralization, beaded ribs, compressed femurs, long bone deformity</td>
<td>AD (new mutations; gonadal mosaicism)</td>
<td>Structural alterations of type I collagen chains—overmodification of type I collagen</td>
<td>COL1A1, COL1A2, CRTAP, P3H1, PPBI, SERPINH1, SP7</td>
</tr>
<tr>
<td>Severe (types III and IV)</td>
<td>Progressively deforming bones, dentinogenesis imperfecta, hearing loss, short stature</td>
<td>AD</td>
<td>Structural alterations of type I collagen chains—overmodification of type I collagen</td>
<td>COL1A1, COL1A2, CRTAP, P3H1, PPBI, FKBP10, SERPINH1, SP7</td>
</tr>
<tr>
<td>V</td>
<td>Similar to severe OI plus calcification of interosseous membrane of forearm, hyperplastic callus formation</td>
<td>AD</td>
<td>None described</td>
<td>Unknown</td>
</tr>
<tr>
<td>VI</td>
<td>Similar to type IV with vertebral compression; mineralization defect</td>
<td>AR</td>
<td>None described</td>
<td>SERPINF1</td>
</tr>
<tr>
<td>VII</td>
<td>Moderate to severe, with fractures at birth, early deformity and rhizomelia</td>
<td>AR</td>
<td>None described</td>
<td>CRTAP</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; CRTAP, cartilage-associated protein; P3H1, prolyl-3-hydroxylase 1; PPBI, cyclophilin B; FKBP10, FK506-binding protein 10; SERPINH1, Serpin Peptidase Inhibitor, Clade H, Member1; SP7, osterix; SERPINF1, Serpin Peptidase Inhibitor, Clade F, Member1.

Although osteopenia with rarefaction of the medullary space and cortical thinning are observed in radiographs, many mild OI cases can be missed on routine radiographic examination and present later in life as individuals with significant osteoporosis. Measurement of bone mineral density by dual-energy x-ray absorptiometry at any age discloses a significant decrease in bone mass. 12 T scores (i.e., standard deviation from the young-adult mean bone mineral density) are frequently in the range of −2.5 to −4.0 at the lumbar spine or proximal femur, consistent with the diagnosis of osteoporosis as defined by the World Health Organization. Low bone mineral density in children with recurrent fractures may assist in identifying children with OI.

**Molecular Pathology**

As in many other OI phenotypes, OI type I or mild OI is the result of mutations affecting the COL1A1(I) and COL1A2(I) polypeptide chains of type I collagen. Cultured fibroblasts from individuals with mild OI synthesize low amounts (approximately one-half) of the expected amounts of type I collagen. The molecular basis for the low production of type I collagen seems to be diminished activity of one of the COL1A1(I) or COL1A2(I) collagen alleles. Many of the reported mutations in OI type I are nonsense and frameshift mutations and are predicted to lead to premature termination codons, although there are some exceptions.13,74

**Lethal Osteogenesis Imperfecta (Type II)**

Approximately 10% of OI patients have the severe neonatal form of the disease, lethal OI. Most cases result from sporadic mutations; however, more recently, recessive forms of the disease have been documented.75-78 These infants present with severe bone fragility, multiple intrauterine fractures at various stages of healing, deformed extremities, and occasionally hydrops fetalis (Figure 105-7). Radiographic features include wormian bones, multiple fractures, crumbling bones, and characteristic beading of the ribs owing to healing callus formation. There is a subtype of the lethal form, OI type IIC, which is autosomal recessive and is differentiated by the absence of beaded ribs (thin ribs) and a different molecular basis of disease.

**Molecular Pathology**

Most cases occur de novo, as new dominant mutations; however, autosomal recessive forms have been established, as has recurrence based on germline mosaicism.79-82 The biochemical abnormality in lethal OI is the inability to synthesize, modify, and secrete normal type I collagen.83 As a result, the amount of type I collagen in bone is low, much of the secreted collagen is abnormally overmodified, and the quantity of the minor collagen types III and V is high. Bone collagen fibers are thinner than normal, and at the intracellular level, type I collagen is retained within dilated endoplasmic reticulum.

Similar to other forms of OI, mutations in the genes encoding COL1A1 and COL1A2 lead to the dominant form or de novo form of lethal OI.84 Single glycine substitutions with the Gly-X-Y triplet of either COL1A1 or COL1A2 lead to this form of OI, as do some small deletions, all producing severe effects on the triple helix. The recessive form accounts for a few of these cases and results from mutations in one of the genes encoding either CRTAP (cartilage-associated protein), P3H1 (prolyl-3-hydroxylase 1), and cyclophilin B (PPBI).75-78 These molecules form a complex that hydroxylates (add an -OH group) to a third position...
residue at proline 986 (Pro986). This modification of a single residue stabilizes the collagen helix.\textsuperscript{15-28} Nonsense or frameshift mutations predicted to lead to premature termination codons and absent function of \textit{CRTAP}, \textit{P3H1}, and \textit{PPBI} produce this form of OI.

\section*{Severely Deforming Osteogenesis Imperfecta (Including Type III and Type IV)}

The deforming variant of OI is the classic form of OI. Similar to lethal OI (OI type II), most cases are inherited as autosomal dominant (or a de novo mutation), although recurrent cases based on autosomal recessive inheritance owing to \textit{CRTAP} or \textit{P3H1} mutations have been described more recently, as well as other recently discovered genes, \textit{FKBP10}, \textit{HSP47}, and \textit{SP7}.\textsuperscript{79-81} This variant is characterized by severe deformity of the limbs and marked kyphoscoliosis, thorax deformity, and significant short stature. The extent of growth retardation is remarkable, and in many adults the height may not surpass 3 feet (90 to 100 cm). Abnormal cranial molding occurs in utero and during infancy, producing frontal bossing and a characteristic triangular-shaped facies. Radiographically, wormian bones and delayed closure of the fontanelles may be observed well into the first decade.

Pulmonary function can be diminished because of distortion of the spine and thorax, and this can progress over time and lead to restrictive lung disease and sleep apnea. Because of diminished vital capacity, pulmonary insufficiency is a leading cause of death in patients with OI type III. Many patients with scoliosis greater than 60 degrees develop respiratory compromise and need pulmonary investigations. Many of these individuals need supplemental oxygen.

Platybasia secondary to soft bone at the base of the skull may cause the external ear canals to slant upward as the base of the skull sinks on the cervical vertebrae; this may lead to communicating or obstructive hydrocephalus, cranial nerve palsies, and upper and lower motor neuron lesions. Headache, diplopia, nystagmus, cranial nerve neuralgia, decline in motor function, urinary dysfunction, and respiratory compromise are complications of basilar invagination.\textsuperscript{85} As opposed to OI type I, most affected OI type III patients have white sclerae as adults. Approximately 25% of patients with autosomal dominant type III OI have dentinogenesis imperfecta, necessitating constant dental care throughout childhood, though this is not true of the recessive forms of this severe form of OI. Severe hearing impairment occurs in 10% of patients, although milder degrees of hearing loss are more common.

The skeleton in these patients has significant osteopenia, leading to multiple fractures in the upper and lower extremities and vertebral bodies, particularly before puberty. In contrast to OI type I, in which fractures tend to heal without deformity, fractures in OI type III frequently lead to skeletal deformity. Radiographs of the skeleton reveal marked osteopenia, thinning of cortical bone, narrowing of the diaphysis, and widening of the metaphysis, which merges into a dysplastic epiphyseal zone filled with whorls of partially calcified cartilage (i.e., popcorn deformity) (see Figure 105-4C). Osteoporosis leads to collapse of vertebral end plates contributing to worsening kyphoscoliosis. Pectus excavatum or pectus carinatum adds to thoracic deformity. In addition, lack of weight bearing increases the severity of osteoporosis and increases the risk of fracture. Many individuals become wheelchair bound at an early age or walk with mechanical assistance.

Clinically, the phenotype of patients with moderately severe OI (OI type IV) falls between the milder and severe forms of OI. In most cases, this form of OI is inherited in an autosomal dominant fashion. Fractures occur rarely at birth, and some patients may not have an initial fracture until later in the first decade. The extent of skeletal deformity involving the spine, thorax, and extremities is usually intermediate between mild and severe, but these patients have short stature and frequently these patients have scoliosis. Patients may have some mild facial dysmorphism and hearing loss. Most fractures occur during childhood and may reoccur during the postmenopausal period in women or in men older than age 50 years. Long bone deformity tends to develop after fractures, which may lead to a difficulty in ambulation. Radiographs of the long bones and vertebral bodies show marked osteopenia with vertebral collapse. Although there is marked cortical thinning, bowing, and coarsening of trabeculae, the overall architecture of the bone is normal (see Figure 105-4B).

\section*{Molecular Pathology}

The molecular basis of OI type III and OI type IV is similar to OI type II. Most cases result from heterozygosity for mutations in \textit{COL1AI} and \textit{COL1A2}.\textsuperscript{86,87} These mutations are glycine substitutions scattered throughout the triple helix and in-frame deletions.\textsuperscript{68} As in OI type II, familial
Undermineralization and overmineralization of bone have been recognized within the same specimen. Bone histomorphology appears relatively normal in OI type I, but osteopenia secondary to thin lamellar plates and diminished cortical width is evident. Immature woven bone and lamellar disarray are characteristic of more severe OI phenotypes.

**Treatment**

Over the years, there have been multiple attempts to treat OI with a variety of vitamins, hormones, and drugs, none of which has been successful. The list includes administration of mineral supplements, fluoride, androgenic steroids, ascorbic acid, and vitamin D. During the past decade, bisphosphonates administered parenterally or orally to children and adults have shown favorable results. The bisphosphonate pamidronate administered intravenously increased bone mass, decreased skeletal pain, and decreased fracture incidence in children with severe OI.

**Osteogenesis Imperfecta Type V (Moderate to Severe)**

OI type V was reported in 2000 as a variant within the heterogeneous group classified under OI type IV. In the initial report of seven OI patients, the phenotype was distinguished by the following criteria: moderate fracture history, hyperplastic callus formation, limitation in forearm pronation and supination as a result of intramembranous bone formation at the joint, normal sclerae, and no dentinogenesis imperfecta. Bone biopsy specimens showed a meshlike appearance of irregularly spaced lamellae, different from the woven bone seen in OI types II, III, and IV. The etiology of this rare form has not been established.

**Osteogenesis Imperfecta Type VI (Moderate to Severe)**

The brittle bone phenotype OI type VI was also reported among the heterogeneous OI type IV group of patients. Characteristic among the eight subjects was the occurrence of a first fracture at an early age (4 to 18 months old). The bone is severely brittle, and affected patients have white sclerae. All patients had vertebral compression fractures, and patients showed elevated serum alkaline phosphatase levels. The gene for this form of OI has been recently identified, pigment epithelium-derived factor (PEDF), also known as serpin F1 (SERPINF1), an antangiogenic protein (unpublished data).

**Osteogenesis Imperfecta Type VII (Moderate to Severe)**

In addition to OI types V and VI, Glorieux reported on an autosomal recessive form of OI and used the designation OI type VII. This form occurred with a small genetic isolate among the First Nations community in northern Quebec, Canada (S89). The phenotype includes fractures at birth, blue sclerae, osteopenia, rhizomelia, and deformities of the lower extremities. The disorder has been localized to chromosome 3p22-24 and has been shown to result from a hypomorphic allele in CRTAP. The identification of the molecular basis of OI type VII changed the molecular view of the basis of disease with the identification of recessively inherited gene defects.

**Histopathology of Bone in Osteogenesis Imperfecta**

The range of histologic appearances of bone in the different OI phenotypes is as variable as the clinical phenotypes. Undermineralization and overmineralization of bone have been recognized within the same specimen. Bone histomorphology appears relatively normal in OI type I, but osteopenia secondary to thin lamellar plates and diminished cortical width is evident. Immature woven bone and lamellar disarray are characteristic of more severe OI phenotypes.
Every child with OI benefits from appropriate rehabilitative therapy. Bracing with lightweight plastics as the child begins to walk can minimize microfracture and bowing of the upper femurs. Muscle-strengthening exercises are essential as primary care and after immobilization for fracture. Perhaps the most beneficial programs have been developed around swimming, preferably in heated pools, and as part of continuous rehabilitative medical care.

EHLERS-DANLOS SYNDROME

The heterogeneous group of disorders grouped together as EDS illustrates the genetic and clinical variability characteristic of the heritable disorders of connective tissue. The most cardinal feature of these disorders is the presence of joint hypermobility, associated with an increase in skin elasticity and skin fragility. In 1997, a simplified classification was proposed dividing EDS into six major clinical types. The classification includes the classic, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis types, as well as several rarer EDS types grouped into “other forms.” Clinically, EDS can be difficult to separate, however, because of considerable overlap in phenotype findings.

**Classic Type**

The classic type of EDS accounts for about 80% of reported cases, and is inherited as an autosomal dominant trait. Originally, EDS was classified as types I and II, and now these types are classified as the classic form, although these subclassifications are still in use. Previously, types I and II EDS were distinguished from each other on the basis of joint laxity and skin fragility, which are less severe in type I than in type II EDS. Most prototypic forms of EDS (Figure 105-8) are characterized by various degrees of hyperextensibility of large and small joints, which are classic findings in EDS. It is crucial that hyperextensibility be defined, and differentiating mild “normal” laxity from hyperextensibility can be challenging. Beighton and colleagues have presented a clinically useful classification of joint laxity (Figure 105-9), as follows:

1. Passive dorsiflexion of the fifth digit beyond 90 degrees = 1 point for each hand
2. Passive apposition of the thumbs to the flexor surface of the radius = 1 point for each hand
3. Hyperextension of the elbows beyond 10 degrees = 1 point for each side
4. Hyperextension of the knees beyond 10 degrees = 1 point for each knee
5. Flexion of the trunk forward so that the palms can be placed flat on the ground = 1 point

A score of 5 or more points is defined as joint hypermobility.

Large joint hyperextensibility is seen in varying degrees in the classic form and decreases with age. Recurrent joint dislocations, periodic joint effusion related to trauma, and the eventual appearance of osteoarthritis pose significant management problems. Bilateral synovial thickening has been observed in EDS, along with the accumulation of small masses of crystalline material in synovial villi. It has been observed that EDS patients constituted 5% of cases in a pediatric arthritis clinic population. There is debate about whether affected infants may be born prematurely to affected mothers because of early rupture of amniotic membranes. Patients with EDS have characteristic facies, with a broad nasal root and epicanthal folds. They may have large, lax ears, and traction on the ears or elbows reveals skin hyperextensibility. Another sign of hypermobility is the ability to touch the tip of the tongue to the nose (Gorlin’s sign). In addition, absence of the lingual frenulum is characteristic for this disorder.

In EDS, the skin has a characteristically pleasant soft or “velvety” feel that can be appreciated by stroking the forearms. Thin, atrophic corrugated and hyperpigmented scars are found on the forehead, under the chin, and on the lower extremities (known as cigarette paper or papyraceous scars), although this is not a uniform finding. Typically, skin lesions heal slowly after injury or surgery. Molluscoid pseudotumors (violaceous subcutaneous tumors ranging in size from 0.5 to 3 cm) may be palpated in tissue over pressure points on the forearms and lower extremities and may be seen on radiographs. Although many patients claim to bruise easily, ecchymoses distributed on the extremities are found only in patients with the more severe forms of the disorder. Severe bilateral varicose veins are a common problem.

Associated pulmonary complications of EDS include spontaneous pneumothorax, pneumomediastinum, and
subpleural blebs.\textsuperscript{107} Mitral valve prolapse and tricuspid valve insufficiency may complicate classic EDS, and aortic root dilation has been reported, although the rate of progression is unknown.\textsuperscript{108,109} Skeletal abnormalities include thoracolumbar kyphoscoliosis; a long, giraffe-like neck; downward sloping of the ribs of the upper part of the thorax; and a tendency toward reversal of the normal cervical, thoracic, and lumbar curves. Anterior wedging of thoracic vertebral bodies is occasionally seen.\textsuperscript{110}

Hypermobility Type

The hypermobile type of EDS is a dominantly inherited disorder that manifests as marked joint and spine hypermobility, recurrent joint dislocations, and the typical soft skin that is neither hyperextensible nor velvety. Individuals with EDS type III may have virtually normal skin. Because of the extent of joint laxity affecting large and small joints, these patients experience multiple dislocations and may require surgical repair. The shoulders, patellae, and temporomandibular joints are frequently sites of dislocation. Musculoskeletal pain may mimic that of fibromyalgia syndrome, and patients frequently seek medical attention for symptoms consistent with chronic pain.

One difficulty in this subtype is differentiating it from benign hypermobility syndrome. Benign hypermobility syndrome is used to describe patients with generalized joint laxity, associated musculoskeletal complaints, but normal skin. They do not have the classic stigmata of either EDS or Marfan syndrome. Many of these patients present in their 20s and 30s with rheumatologic symptoms that can pose problems in diagnosis and treatment. The precise approach and treatment for these patients are unclear.

Structure and Molecular Pathology of the Classic and Hypermobile Types of Ehlers-Danlos Syndrome

Abnormally large, small, or frayed dermal collagen fibrils and disordered elastic fibers have been observed in the classic and hypermobile forms of EDS by electron microscopy.\textsuperscript{111} Type V collagen is a heterotrimeric collagen composed of the products of three genes: COL5A1(V), COL5A2(V), and COL5A3(V). Type V collagen may stabilize type I collagen by co-assembling with that protein. Initially, linkage analysis was used to show that some families with the classic form of EDS (originally types I and II) were linked to COL5A1. Subsequently, it has been established that about 50% of patients with either the classic or hypermobility type of EDS have mutations in COL5A1(V) or COL5A2(V). There seems to be no genotype-phenotype correlation in these disorders, and no mutations have been identified in COL5A3(V). In some cases of EDS classic type, heterozygosity for mutations in COL1A1(I) has been shown.\textsuperscript{112}

Vascular Type

The vascular type of EDS, an autosomal dominant disorder, is one of the most severe forms of EDS and was formerly referred to as EDS type IV. It is associated with arterial rupture, commonly involving iliac, splenic, or renal arteries or the aorta and resulting in either massive hematomas or death.\textsuperscript{113} Arterial rupture may lead to stroke or intracranial bleeding in a limb. Patients with vascular EDS also are susceptible to rupture of internal viscera and may experience repeated rupture of diverticula on the antimesenteric border of the large bowel. Problems with pregnancy vary from preterm delivery to uterine or vascular rupture, although delivery is uneventful in many instances.\textsuperscript{114} Typical causes of death in EDS families have included gastrointestinal rupture, peripartum uterine rupture, rupture of the hepatic artery, and vascular ruptures.

In contrast to the other forms of EDS, EDS type IV is not associated with hyperextensibility of large joints, although small joints may be minimally hypermobile. These patients have thin, soft, transparent skin, through which a prominent venous pattern is seen, especially on their chest walls. Their skin is not velvety as in the classic form. Excessive bruising may occur. Vascular EDS includes, as a subgroup, patients who have been described as acrogeric—having characteristically thin faces, prominent eyes, and extremities that lack subcutaneous fat, giving the appearance of premature aging. Peripheral joint contractures and acro-osteolysis have been described.

Spontaneous hemopneumothorax associated with hemoptysis and mitral valve prolapse occurs frequently. Surgical repair of ruptured vessels or internal viscera is extremely difficult because of friable tissues. Anesthetic and surgical difficulties related to intubation, spontaneous arterial bleeding during surgery, and ligation of vessels that tear under pressure complicate surgical maneuvers. Similarly, arteriography may be dangerous in these individuals. These patients
can be quite difficult to manage. Imaging studies may reveal normal-appearing aorta or other large vessels that rupture shortly after a “normal study.”

**Molecular Pathology**

Although EDS type IV was clinically recognized as a disorder distinct from the other forms of EDS, the finding that tissues from these individuals were deficient in type III collagen clearly distinguished this as a separate form of EDS. Type III collagen is a homotrimer [1(III)3] found in skin, blood vessels, and the walls of hollow viscera. Heterozygosity for mutations in the gene encoding COL3A1 leads to EDS vascular type and affects the synthesis and secretion of type III collagen. Various types of mutations have been identified including missense, nonsense, and deletions, and there is no correlation between the clinical phenotype and type III collagen mutation. In this disorder, the biochemical abnormalities include decreased or absent type III collagen or production of an abnormal homotrimer that is retained in the endoplasmic reticulum and, if secreted, contributes to abnormal matrix. Biochemical and mutational analysis for this disorder is available (GeneTests) and should be considered because this is dominantly inherited.

**Therapy in Classic, Hypermobility, and Vascular Types of Ehlers-Danlos Syndrome**

There are no specific treatments for the classic, hypermobility, and vascular forms of EDS. Supportive therapy is essential, however, for preservation of normal joint function and alleviation of joint pain. Planned exercise programs and muscle strengthening exercises are useful and do much to maintain a positive outlook in these individuals, who may have a poor prognosis if joint stability and articular surfaces are compromised by excessive activity or chronic trauma. Many children and young adults with large joint hypermobility are attracted to activities such as gymnastics and dance, and these activities promote hypermobility and joint damage. The presence of multiple ecchymoses raises concern about a bleeding diathesis, particularly at the time of elective surgery. Although there is no consistent basis for the hemorrhagic tendency in the classic and hyperextensibility forms of EDS, anecdotally, these patients tend to have greater blood losses than expected at surgery. In our center, we discourage pregnancy in patients with the vascular form because the mortality rate is increased.

**Arthrochalasia Type**

Formerly known as EDS types VIIA and VIIB, the arthrochalaasia type of EDS is another autosomal dominant form resulting from mutations that cause faulty processing of type I collagen at the N-terminus. The arthrochalasia type of EDS is characterized by pronounced and generalized joint hypermobility, moderate cutaneous elasticity, moderate bruising, a characteristic round facies with midface hypoplasia, and significant short stature. The skin has a doughy feel and is fragile and hyperelastic. Kyphoscoliosis and muscle hypotonia are frequently present. These patients experience multiple dislocations, particularly involving large joints including the hips, knees, and ankles. These dislocations manifest in the newborn period, especially hip and ankle dislocations. Patients frequently need orthopedic surgery for joint dislocation, and their tissues are highly friable, which complicates orthopedic procedures.

**Molecular Pathology**

The two disorders EDS types VIIA and VIIB, now termed arthrochalasia type, result from mutations involving the N-terminal propeptide cleavage site of type I collagen. The arthrochalasia type of EDS has provided insight into the process of normal type I collagen fiber formation. The initial observation was of an accumulation of unprocessed procollagen within the dermis of affected individuals. With subsequent recognition that procollagen had N-terminal and C-terminal extension propeptides, and that separate enzymes were responsible for their removal, the syndrome became more sharply defined as an accumulation of procollagen with the N-terminal peptides still attached (pN collagen). Of the two distinctly different genetic abnormalities resulting in procollagen accumulation, the more frequent form is the mutational resistance of a procollagen cleavage site to the action of the N-terminal procollagen peptidase. The resistance results from an amino acid substitution or deletion in the proCOL1A1 (EDS type VIIA) or pro2COL2A1 (EDS type VIIB) chain, leading to a portion of the collagen chains containing an abnormal N-terminal extension; this results from mutations in COL1A1 or COL1A2 in exon 6 of the molecule, which alters the proteinase cleavage site. Individuals with mutations in exon 6 of COL1A1 are more severely affected than individuals with similar mutations in COL1A2.

**Dermatosparaxis Type**

The dermatosparaxis type of EDS was formerly known as EDS type VIIIC and is an autosomal recessive form of EDS. In this type, the skin is extremely fragile, soft, and doughy with easy bruising. The phenotype includes blue sclerae, marked joint hypermobility, micrognathia, large umbilical hernia, epiphysial delay, and mild hirsutism. The dermatosparaxis type results from a deficiency of the procollagen N-propeptidase, in contrast to the arthrochalasia form, which involves the enzyme cleavage site, and individuals have been identified who are homozygous for mutations in the gene. This defect is homologous to the dermatosparaxis defect in sheep and cattle.

**Kyphoscoliosis Type**

The kyphoscoliosis type of EDS, formerly known as EDS type VI, is inherited as an autosomal recessive disease. The findings in this disorder include severe kyphoscoliosis noted at birth, recurrent joint dislocations, hyperextensible skin and joints, poor tone, and reduced muscle mass. The skin is grossly abnormal and has been described as pale, translucent, and velvety; on trauma, the skin shows gaping wounds that heal poorly. One difference in this form of EDS is that there is significant ocular involvement. Affected individuals have microcornea, retinal detachment, and glaucoma leading to blindness in some individuals. In addition, patients with severe kyphoscoliosis may develop respiratory
and cardiac compromise and ultimately cardiorespiratory failure.

**Molecular Pathology**

The kyphoscoliosis type of EDS results from lysyl hydroxylase deficiency. A variety of mutations within the lysyl hydroxylase gene have been defined and include premature stop codons, amino acid substitutions, internal deletions, and compound heterozygotes. Defective lysyl hydroxylase impairs the conversion of lysyl residues to hydroxylsine on procollagen peptides. The consequence of deficient hydroxylsine content of collagen is the effect it has on cross-linking, which helps stabilize the mature collagen molecule.

**Other Ehlers-Danlos Syndrome Types**

Numerous other rare forms of EDS have some overlap with other disorders or have been reported only in a small cohort of individuals, and these are not discussed in this chapter.

**MARFAN SYNDROME**

One of the most common inherited disorders of connective tissue, Marfan syndrome is an autosomal dominant disorder with a reported incidence of 1 in 10,000 to 20,000 individuals. Clinical presentations range from the severe infantile form to individuals who are only mildly affected. Although the most impressive findings in Marfan syndrome are relative to the musculoskeletal, cardiac, and ocular findings, affected individuals also have pulmonary, neurologic, and psychological complications. Marfan syndrome also has become one of the few genetic disorders for which there has been advocacy for treatment to slow the progression of the disease, and physicians need to recognize the phenotype because many affected individuals present with life-threatening emergencies.

**Clinical Features**

Marfan syndrome can be difficult to diagnose in some individuals and families, and it has been recognized that it has also been overdiagnosed. Stringent criteria for this diagnosis were proposed in 1996. The 1996 criteria rely on the recognition of “major” and “minor” clinical manifestations involving the skeletal, cardiovascular, dura, and ocular systems (excellent review in GeneReviews, Marfan syndrome). Major criteria include four of eight typical skeletal manifestations, ectopia lentis, aortic root dilation involving the sinuses of Valsalva or aortic dissection, and lumbosacral dural ectasia by computed tomography or MRI. Major criteria for establishing the diagnosis in a family member include having a parent, child, or sibling who meets major criteria independently, and the presence of a fibrillin-1 mutation known to cause the syndrome identified in a familial Marfan syndrome patient.

Establishing the diagnosis unequivocally in the absence of a family history requires a major manifestation from two systems and involvement of a third system. If a mutation known to cause Marfan syndrome is identified, the diagnosis requires one major criterion and involvement of a second organ system. The reason is that there is a great deal of intrafamilial variability in this disorder, and there are individuals who harbor heterozygosity for mutations but do not meet criteria for Marfan syndrome and may have different prognoses. Similar to other connective tissue disorders, there is wide variability in phenotypic expression.

Aortic disease leading to the formation of aneurysmal dilation and dissection is the main cause of morbidity and mortality in Marfan syndrome. Dilation of the aorta is found in 50% of children and progresses over time. Echocardiography shows that 60% to 80% of adult patients have dilation of the aortic root that may involve other segments of the thoracic aorta, the abdominal aorta, or even the carotid and intracranial arteries. Dissection usually begins above the coronary ostia and extends the entire length of the aorta. Of Marfan syndrome patients, 60% to 70% have mitral valve prolapse with regurgitation. Heart failure and myocardial infarction may complicate the course of Marfan syndrome patients. Pregnant women are at particular risk for aortic dissection, particularly women who already have aortic root dilation, and this should be taken into consideration when treating a woman of reproductive age with Marfan syndrome.

Arachnodactyly occurs in 90% of patients. Following are techniques that aid in determining arachnodactyly (Figure 105-10):

1. The thumb: The Steinberg test is positive when the thumb, enclosed in the clenched fist, extends beyond the hypothenar border.
2. The wrist: The Walker-Murdoch sign is positive when there is overlap of the thumb and fifth digit as they encircle the opposite wrist.
3. The metacarpal: The metacarpal index is done by radiographic determination and is the mean value of the lengths divided by the midpoint widths of the second, third, and fourth metacarpals. In normal subjects, the metacarpal index ranges from 5.4 to 7.9, whereas this range is 8.4 to 10.4 in patients with Marfan syndrome.

Thoracic kyphosis may be associated with reduced lung capacity and residual volume that may lead to pulmonary insufficiency. Dural ectasia, which may occur in 40% of patients, results from enlargement of the spinal canal owing to progressive ectasia of the dura and neural foramina and erosion of vertebral bone; this usually involves the lower spine. Diminished bone mineral density has been reported in several patients with Marfan syndrome. Ectopia lentis occurs in 50% to 80% of patients with Marfan syndrome. Subluxation of the lens is usually bilateral and appears by age 5 years. Although the lens is typically displaced upward, displacement into any quadrant may occur. Visual acuity is diminished in many patients because of lens subluxation or secondary acute glaucoma. Secondary myopia, retinal detachment, and iritis with loss of vision contribute to most of the ocular-related morbidity.

Marfan syndrome patients have been found to develop large epidural venous plexuses in the lumbar and cervical regions, a major diagnostic criterion for the syndrome. These engorged venous plexuses, which are visualized by MRI myelography, have been associated with the syndrome of spontaneous intracranial hypotension, which is also
associated with dural tears. Clinical signs are severe headache, back and leg pain, radiculopathies, and incontinence secondary to cerebral displacement. Spinal abnormalities in Marfan syndrome include increased interpedicle distance of nonrotated vertebrae, vertebral inversion (flattening of the normal kyphosis at the dorsal level and kyphosis or disappearance of the physiologic lordosis at the lumbar level), and vertebral dysplasia (dolichospondylic, elongated vertebral bodies with increased concavity). Scoliosis constitutes one of the major management problems in Marfan syndrome. In one series, the average age of onset was 10.5 years (range, 3 to 15 years), with rapid progression during adolescence. If mechanical bracing or physical therapy fails to halt progression, spinal fusion should be considered, particularly when the curvature exceeds 45 to 50 degrees.

Differential Diagnosis: Homocystinuria

Homocystinuria, which shares several skeletal and ocular features with Marfan syndrome, is the prime diagnostic consideration. Homocystinuria is an autosomal recessive disease. The characteristic features of this metabolic disorder of sulfur metabolism are marfanoid phenotype with joint laxity, scoliosis, lens dislocation, early-onset osteoporosis, vascular thrombosis affecting arteries and veins owing to increased clotting activity and the cytotoxic effect of homocysteine on vascular endothelial cells, and mild mental retardation.

Cystathionine β-synthase deficiency is the most common cause of homocystinuria. Affected individuals have elevated levels of homocysteine and methionine, whereas cystathionine and cysteine levels in blood are decreased. This disorder is differentiated from Marfan syndrome because the direction of ectopia lentis is different than in Marfan syndrome, and there is no progressive aortic root dilation.

Molecular Biology of Marfan Syndrome

Fibrillin-1 protein is an important component of elastic and nonelastic connective tissues throughout the body. It is the main protein of a group of connective tissue microfibrils that are essential for normal elastic fibrillogenesis. In nonelastic tissues, the fibrillin-1-containing microfibril functions as an anchoring fiber. FBN-1 is a large gene (65 exons) located at chromosome 15q21.1. Since the first report of an FBN-1 mutation in Marfan syndrome in 1991, more than 500 different FBN-1 mutations have been described in Marfan syndrome and related disorders. FBN-1 mutations occur across a wide range of milder phenotypes that overlap the classic Marfan phenotype including dominantly inherited ectopia lentis, Shprintzen-Goldberg syndrome, and familial or isolated forms of aortic aneurysms. Most of these are private mutations (occur genetically independent with no “hot spot” in the molecule). The one exception is the rare infantile Marfan syndrome mutations that cluster between exons 24 and 26 and exon 32. Heterozygosity for missense, frame-shifts, deletions and insertions, splice site alterations, and nonsense mutations all have been seen. Robinson and colleagues stated that at least 337 mainly unique mutations in the FBN-1 gene had been reported in Marfan syndrome up to that time. The clinical presentation of the fibrillinopathies caused by FBN-1 mutations ranged from isolated ectopia lentis to neonatal Marfan syndrome, which generally leads to death within the first 2 years of life.
Treatment

In 1972, the life span of untreated patients with classic Marfan syndrome was about 32 years. The early mortality in Marfan syndrome results primarily from complications associated with aortic dilation. This symmetric dilation of the sinuses of Valsalva is progressive throughout life and is often detectable in infancy. In the early 1970s, there was discussion on attempting to reduce the risk of aortic dissection in patients with Marfan syndrome. Shores and colleagues reported on a 10-year open-label trial of propranolol in 70 patients with Marfan syndrome. When compared with the control group, the treated individuals had a significantly slower rate of dilation of the aortic root, improved survival, and fewer treated patients reaching a clinical endpoint (death, congestive heart failure, aortic regurgitation, aortic dissection, or cardiovascular surgery).

More recent data generated from a mouse model of Marfan syndrome suggest excessive signaling by the transforming growth factor transforming growth factor (TGF)-β family of cytokines. There is evidence that aortic aneurysm in the mouse model of Marfan syndrome is associated with increased TGF-β signaling and TGF-β antagonists such as TGF-β-neutralizing antibody or the angiotensin II type 1 receptor blocker, losartan. In this mouse model, losartan (angiotensin II type 1 blockade) fully corrected the abnormalities in the aortic wall. There was some evidence that alveolar septation, which contributes to pulmonary problems in Marfan syndrome, was partially reversed with losartan treatment. Because this drug is in clinical use for hypertension, it could merit further investigation as a preventive treatment in Marfan syndrome. Clinical trials are now under way testing the use of losartan in Marfan syndrome and many individuals with Marfan syndrome are using losartan outside of clinical trials.

Electrocardiogram monitoring is done yearly until the aortic root diameter exceeds 45 mm, at which time monitoring is done every 6 months. Elective repair of aortic root disease before enlargement to 6 cm has occurred is preferable to emergency repair required for marked dilation or dissection. Surgical intervention is considered when the aortic root diameter approaches twice the upper limit of normal for body surface area, or the absolute measurement exceeds 50 to 55 mm. Total aortic root replacement with a composite valve graft (Bentall procedure) and coronary artery implantation become the surgical procedures of choice and are associated with an 81% 10-year survival rate and a 75% 20-year survival rate. Mitral valve replacement and coronary artery implantation may be accomplished during the same procedure. Most importantly, repeated trials have shown that patients who undergo elective repair, as opposed to emergent repair, do substantially better.

Correction of scoliosis may be attempted with bracing; however, surgical repair should be considered when the curve exceeds 40 degrees. Progressive scoliosis in Marfan syndrome may require fixation with rods, and complications of joint laxity may require orthopedic correction. Arthropathy associated with excessive joint mobility may require orthopedic intervention. Dislocated lenses should not be removed surgically, unless more conventional means of correcting vision are ineffective.

LOEYS-DIETZ SYNDROME

In 2005, Loey and colleagues described individuals with a previously undescribed autosomal dominant aortic aneurysm syndrome. This disorder, now referred to as Loey-Dietz syndrome, is also characterized by hypertelorism, bifid uvula or cleft palate or both, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. Other abnormal findings include craniosynostosis, structural brain abnormalities, mental retardation, congenital heart disease, and aneurysms with dissection throughout the arterial tree.

Some individuals with Loey-Dietz syndrome had a clinical phenotype that overlapped with Marfan syndrome, but none met diagnostic criteria set forth in 1996. Although Marfan syndrome is associated with progressive arterial disease, in Loey-Dietz syndrome the aneurysms tended to be particularly aggressive and rupture at an earlier stage and size than seen in Marfan syndrome. Heterozygosity for mutations in TGFB1 and TGFB2 has been identified. From a management perspective, it is important to recognize these individuals because they are managed more aggressively than patients with Marfan syndrome. Aortic aneurysms are corrected at smaller sizes (4 cm), and complaints such as abdominal pain and headache should be thoroughly investigated because they may be associated with aneurysms.

CONGENITAL CONTRACTURAL ARACHNODACTYLY

Congenital contractural arachnodactyly is an autosomal dominant condition that includes tall stature, arachnodactyly, dolichostenomelia, and multiple contractures involving large joints. There is a characteristic "crumpled ear" deformity as a result of a flattened helix with partial obliteration of the concha. Marked deformity of the chest cage also occurs, and scoliosis may be progressive and severe. For unknown reasons, the contractures tend to become less severe with age. Radiographically, osteopenia can be seen. The ocular and typical cardiac lesions of classic Marfan syndrome are absent. This disorder results from heterozygosity for mutations in fibrillin-2 (FBN2). There are many other extremely rare disorders of connective tissue, especially with profound effects on the skin including the group of disorders termed cutis laxa and pseudoxanthoma elasticum.

SUMMARY

Heritable disorders of connective tissues are a heterogeneous group of disorders characterized by abnormalities in skeletal tissues including cartilage, bone, tendon, ligament, muscle, and skin. The clinical spectrum ranges from extreme short stature to excessively tall individuals, and the types of altered genes span all of the numerous gene families and pathways. Affected individuals usually need medical attention their entire lives and have been victims of appearing different because they cannot mask their abnormalities. Understanding and appreciation for the unique set of medical issues in each disorder would improve these individuals' quality of life and their life span.
Selected References


Full references for this chapter can be found on www.expertconsult.com.
References


