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by short bulbous roots, pulp calcification, and radicular dentin depos ited in swirls. The disorder is caused by gene mutations in GALNT3, FGF23, or α-Klotho, leading to FGF23 deficiency or resistance. The reduced activity of FGF23 leads to increased renal tubular reabsorption of phosphate, elevated serum phosphate, and spontaneous soft tissue calcification from elevated calcium-phosphate concentration product. The disease usually presents in childhood and continues throughout the patient’s life. The calcific masses are typically painless and grow at variable rates, sometimes becoming large and bulky. The masses are often located near major joints but remain extracapsular. Joint range of motion is not usually restricted unless the tumors are very large. Com plications include compression of neural structures and ulceration of the overlying skin with drainage of chalky fluid and risk of secondary infection. Small deposits not detected by standard radiographs may be detected by 99mTc bone scanning. The most common laboratory findings are hyperphosphatemia and elevated serum 1,25-dihydroxyvitamin D levels. Serum calcium, parathyroid hormone, and ALP levels are usually nor mal. Renal function is also usually normal. Urine calcium and phosphate excretions are low, and calcium and phosphate balances are positive. An acquired form of the disease may occur with other causes of hyperphosphatemia, such as secondary hyperparathyroidism associ ated with hemodialysis, hypoparathyroidism, pseudohypoparathyroid ism, and massive cell lysis following chemotherapy for leukemia. Tissue trauma from joint movement may contribute to the periarticular cal cifications. Metastatic calcifications are also seen in conditions associ ated with hypercalcemia, such as in sarcoidosis, vitamin D intoxication, milk-alkali syndrome, and primary hyperparathyroidism. In these con ditions, however, mineral deposits are more likely to occur in protontransporting organs such as kidney, lungs, and gastric mucosa in which an alkaline milieu is generated by the proton pumps. TREATMENT Tumoral Calcinosis Therapeutic successes have been achieved with surgical removal of subcutaneous calcified masses, which tend not to recur if all calci fication is removed from the site. Reduction of serum phosphate by chronic phosphorus restriction may be accomplished using low dietary phosphorus intake alone or in combination with oral phos phate binders. The addition of the phosphaturic agent acetazol amide may be useful. Limited experience using the phosphaturic action of calcitonin deserves further testing. ■ ■DYSTROPHIC CALCIFICATION Posttraumatic calcification may occur with normal serum calcium and phosphate levels and normal ion-solubility product. The depos ited mineral is either in the form of amorphous calcium phosphate or

hydroxyapatite crystals. Soft tissue calcification complicating con nective tissue disorders such as scleroderma, dermatomyositis, and systemic lupus erythematosus may involve localized areas of the skin or deeper subcutaneous tissue and is referred to as calcinosis circum scripta. Mineral deposition at sites of deeper tissue injury including periarticular sites is called calcinosis universalis. ■ ■ECTOPIC OSSIFICATION True extraskeletal bone formation that begins in areas of fasciitis following surgery, trauma, burns, or neurologic injury is referred to as myositis ossificans. The bone formed is organized as lamellar or trabecular, with normal osteoblasts and osteoclasts conducting active remodeling. Well-developed haversian systems and marrow elements may be present. A second cause of ectopic bone formation occurs in an inherited disorder, fibrodysplasia ossificans progressiva. ■ ■FIBRODYSPLASIA OSSIFICANS PROGRESSIVA This is also called myositis ossificans progressiva; it is a rare autosomal dominant disorder characterized by congenital deformities of the hands and feet and episodic soft tissue swellings that ossify. The disor der is caused by an activating mutation in activin receptor A type 1. Ectopic bone formation occurs in fascia, tendons, ligaments, and connective

tissue within voluntary muscles. Tender, rubbery induration, some times precipitated by trauma, develops in the soft tissue and gradually calcifies. Eventually, heterotopic bone forms at these sites of soft tissue trauma. Morbidity results from heterotopic bone interfering with nor mal movement and function of muscle and other soft tissues. Mortality is usually related to restrictive lung disease caused by an inability of the chest to expand. Laboratory tests are unremarkable.

Until recently, there was no effective approved medical therapy. Bisphosphonates, glucocorticoids, and a low-calcium diet have largely been ineffective in halting progression of the ossification. Palovaro tene has been shown to reduce new heterotopic ossification by 60% versus historical controls but increased premature epiphyseal closure in children. In 2023, the therapy was approved in the United States for females over age 8 and males over age 10. Another potential therapeu tic option, REGN2477 (also known as garetosmab), an anti–activin A antibody, is in clinical trials. Surgical removal of ectopic bone is not recommended because the trauma of surgery may precipitate forma tion of new areas of heterotopic bone. Dental complications, including frozen jaw, may occur following injection of local anesthetics. Heritable Disorders of Connective Tissue CHAPTER 425 Acknowledgment The authors acknowledge the contribution of Dr. Murray J. Favus to this chapter in previous editions of Harrison’s. ■ ■FURTHER READING Boyce AM, Collins MT: Fibrous dysplasia/McCune-Albright syn drome: A rare, mosaic disease of Gαs activation. Endocr Rev 41:345, 2020. De Castro LF et al: Safety and efficacy of denosumab for fibrous dys plasia of bone. N Eng J Med 388:8, 2023. Pognolo RJ et al: Reduction of new heterotopic ossification (HO) in the open-label, phase 3 MOVE trial of palovarotene for fibrodysplasia ossificans progressive (FOP). J Bone Miner Res 38:3, 2022. Ralston SH et al: Diagnosis and management of Paget’s disease of bone in adults: A clinical guideline. J Bone Miner Res 34:579, 2019. Shapiro JR, Lewiecki EM: Hypophosphatasia in adults: Clinical assessment and treatment considerations. J Bone Miner Res 32:1977, 2017. Singer FR et al: Paget’s disease of bone: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 99:4408, 2014. Tan A et al: Long-term randomized trial of intensive versus symptom atic management in Paget’s disease of the bone: The PRISM-EZ Study. J Bone Miner Res 32:1165, 2017. Wu CC et al: Diagnosis and management of osteopetrosis: Consensus guidelines from the osteopetrosis working group. J Clin Endocrinol Metab 102:3111, 2017. Section 5 Disorders of Intermediary Metabolism Joan C. Marini, Fransiska Malfait

Heritable Disorders of Connective Tissue CLASSIFICATION OF CONNECTIVE

TISSUE DISORDERS Some of the most common conditions that are transmitted genetically in families are disorders that produce clinically obvious changes in the bone, cartilage, skin, or relatively acellular tissues such as tendons

that have been loosely defined as connective tissues. Because of their heritability, some of the disorders were recognized as potentially traceable to mutated genes soon after the principles of genetics were introduced into medicine by Garrod and others. About half a century later, McKusick emphasized the specificity of many of the diseases for selective connective tissues and suggested that they were probably caused by mutations in genes coding for the major proteins found in those tissues. In the past several decades, mutations in several hundred different genes expressed in connective tissues have been identified as the cause of many connective tissue disorders. However, classifying the disorders on the basis of either their clinical presentations or the mutations causing them continues to present a challenge for both the clinician and the molecular biologist.

PART 12 Endocrinology and Metabolism Information on the disorders has continued to develop on two levels. The initial clinical classifications suggested by McKusick and many others had to be refined as more patients were examined. For example, some patients had skin changes similar to those commonly seen in Ehlers-Danlos syndrome (EDS), but this feature was overshad owed by other features such as extreme hypotonia or sudden rupture of large blood vessels. To account for the full spectrum of presentations in patients and families, many of the disorders have been reclassified several times, dividing each into a series of subtypes. The identification of mutations causing the diseases has developed on a parallel track. The first genes cloned for connective tissues were the two genes coding for type I collagen (COL1A1 and COL1A2), the most abundant protein in bones, skin, tendons, and several other tis sues. This facilitated early studies in patients with osteogenesis imper fecta (OI) that revealed mutations in type I collagen genes. Biochemical data, developed primarily with cultures of skin fibroblasts from affected individuals, demonstrated that the mutations dramatically altered the synthesis of collagen α-chains or the structure of collagen fibers. The results stimulated efforts to identify additional mutations in genes cod ing for structural proteins. Genes for collagens provided an attractive paradigm to search for mutations, since a series of different types of collagens were found in different connective tissues and the collagen genes were readily isolated by their unique signature sequences. Also, the collagen genes were vulnerable to a large number of different muta tions because of unusual structural requirements of the protein. The search for mutations in collagen genes proved fruitful in that mutations were found in most patients with OI, in many patients with hyperex tensible skin and hypermobile joints, in some patients with dwarfism, and in patients with other disorders, including some such as Alport syndrome (AS) that were not initially classified as disorders of con nective tissue. Also, mutations in collagen genes were found in subset of patients presenting with osteoarthritis (OA) or osteoporosis, likely representing the mildest end of the syndromic spectrum. However, the search for mutations quickly expanded to hundreds of other genes that included genes for other structural proteins, for the posttranslational modification and processing of the structural proteins, for chaperones, and for growth factors and their receptors and other genes whose func tions are still not fully understood. In many instances, the mutations helped to define the clinical sub type of the disorder, while in others, they revealed the genetic hetero geneity of

the same clinical presentations. Conversely, some patients with different manifestations were found to have mutations in the same genes. In noncollagenous genes, it was sometimes difficult to establish whether a change in the structure of a gene caused the phenotypic changes in the patients or was simply a neutral polymorphism. There fore, there has been a continuing debate as to whether the disorders should be classified by their clinical presentations or by the causative genes. As an illustration of the problems, mutations in 552 genes have now been found associated with 771 defined disorders of the skeleton. The latest (2023) nosology for the disorders, which adopted a dyadic naming system, systematically associating a phenotypic entity with the gene it arises from, remains “hybrid” in nature in the sense that the classification is not always based on the same criteria. Some dis eases are grouped based on the causal gene, others are listed together, because they share common radiographic features, and still others are brought together because of a similar clinical course (lethality) or

involvement of similar parts of the skeleton. A simpler system of clas sification proved feasible for one rare heritable disorder of skin, epider molysis bullosa. The disorder was first defined clinically into subtypes based on the layers of the skin that were cleaved in friction-induced blisters. Most patients in each subtype were subsequently shown to have mutations in genes expressed in the corresponding layer of skin. Even with these patients, the strength of the genotype-phenotype cor relation varies and mutations have not yet been found in every patient. The best pathway through this maze of information is probably to begin by matching the signs and symptoms in a patient with the pre sentations that define each clinical classification. A major focus should be on the most common disorders, recognizing that the signs and symptoms may vary among different individuals and family members with the same diagnosis. Then, attempt to reach a decision, in consul tation with the patient, parents, and specialist, as to whether a DNA analysis for the probable mutation is indicated. Among the consider ations are the cost, the rigor with which the clinical classification has been linked to mutated genes, the reassurance the diagnosis can bring to patients and their families, the use of the genetic information for prenatal diagnosis, and the possibility that mutation-specific therapies may be developed in the future. For individuals affected with these dis orders, consulting a specialist in the disease is highly recommended to determine a multidisciplinary program for management and therapy. Patient support groups have formed for many of the diseases and are an important source of information. Patients with the most common forms of the disorders have muta tions in a limited number of genes. This chapter will focus primarily on these. Also, it will provide a brief summary of biosynthesis and structure of connective tissues that may help guide the physician from the nature of the mutations to their clinical presentations. ■ ■COMPOSITION OF CONNECTIVE TISSUES Connective tissues such as skin, bone, cartilage, ligaments, and ten dons are the critical structural frameworks of the body. They consist of a complex interacting extracellular matrix network of collagens, proteoglycans, and a large number of noncollagenous glycoproteins and proteins. While these precise combinations of up to ~500 potential extracellular matrix building blocks, collectively called “the matri some,” provide tissue-specific function, there are many overarching similarities in composition such as the role of composite collagen fibrils in providing strength and form, elastin fibrils and proteoglycans and other interacting proteins, and glycoproteins that fine-tune function (Table 425-1). The most abundant components of many connective tissues are three similar fibrillar collagens (types I, II, and III). They have a similar tensile strength that is comparable to that of steel wires. The three fibrillar collagens are distributed in a tissue-specific manner: type I collagen accounts for most of the protein of dermis, ligaments, tendons, and demineralized bone; type I and type III are the most

abundant proteins of large blood vessels; and type II is the most abun dant protein of cartilage. ■ ■BIOSYNTHESIS AND TURNOVER OF

CONNECTIVE TISSUES Connective tissues are among the most stable components in living organisms, but they are not inert. During embryonic development, connective tissue membranes appear as early as the four-cell blastocyst to provide a structural scaffold for the developing embryo. With the development of blood vessels and skeleton, there is a rapid increase in the synthesis, degradation, and resynthesis of connective tissues. The turnover continues at a slower, but still rapid pace throughout postnatal development and then spikes during the growth spurt of puberty. During adulthood, the metabolic turnover of most connective tissues is slow, but it continues at a moderate pace in bone. With age, malnutrition, physical inactivity, and low gravitational stress, the rate of degradation of most connective tissues, especially in bone and skin, begins to exceed the rate of synthesis and the tissues shrink. In starva tion, a large fraction of the collagen in skin and other connective tissues is degraded and provides amino acids for gluconeogenesis (Chap. 345). In both OA and rheumatoid arthritis, there is extensive degradation of

TABLE 425-1 Constituents of Connective Tissues and Their Associated Heritable Conditions PROTEIN TISSUE DISTRIBUTION DISEASE KEY MANIFESTATIONS Collagen I Bone, cornea, dermis, tendon Osteogenesis imperfecta Bone fragility with fractures and deformity; blue sclerae; dentinogenesis imperfecta; hearing loss EDS (various rare types) Joint hypermobility; skin hyperextensibility; skin fragility; soft connective tissue fragility Caffey disease Subperiosteal new bone formation; soft tissue swelling; fever and irritability Collagen II Cartilage, vitreous Various chondrodysplasias Skeletal dysplasia; ocular manifestations; hearing loss; orofacial findings Collagen III Dermis, aorta, uterus, intestine Vascular EDS Arterial, intestinal, and uterine fragility; thin translucent skin; easy bruising Collagen IV Basement membranes Alport syndrome (COL4A3/A4/A5) Hematuria; hearing loss; ocular abnormalities Brain small-vessel disease (COL4A1/A2) Porencephaly; intracerebral hemorrhage; retinal arterial tortuosity; (congenital) cataract; Axenfeld-Rieger anomaly; hematuria; renal cysts; muscle cramps Collagen V Placental tissue, bone, dermis, cornea Classic EDS Joint hypermobility; skin hyperextensibility; atrophic scarring Collagen VI Uterus, dermis, cornea, cartilage Bethlem myopathy and Ullrich congenital muscular dystrophy Collagen VII Skin, amniotic membrane, mucosal epithelium Dystrophic epidermolysis bullosa Skin blistering; oral and esophageal blistering; corneal erosions Collagen VIII Descemet’s membrane, endothelial cells Corneal dystrophy Corneal endothelial dystrophy; stromal edema Collagen IX Cartilage, vitreous Stickler syndrome Spondyloepiphyseal dysplasia; early-onset osteoarthritis; high myopia; vitreoretinal abnormalities; hearing loss; cleft palate; midfacial hypoplasia Collagen X Calcifying cartilage Multiple epiphyseal dysplasia Epiphyseal dysplasia; early-onset osteoarthritis Collagen XI Cartilage, intervertebral disk Various chondrodysplasias Skeletal dysplasia; ocular manifestations; hearing loss; orofacial findings Collagen XII Dermis, tendon, cartilage Myopathic EDS Joint hypermobility; congenital muscle hypotonia and/or atrophy; proximal joint contractures Collagen XVII Corneal epithelial cells Junctional epidermolysis bullosa Blistering of the skin and mucosae (mild to severe) Collagen XVIII Pia, blood vessels of the developing human cerebral cortex Knobloch syndrome Early-onset severe myopia; vitreoretinal degeneration with retinal detachment; hydrocephalus; structural brain defects; epilepsy; cognitive dysfunction Collagen XXVII Chondrocytes, epithelial cell layers in developing tissues, including stomach, lung, gonad, skin, cochlea, and tooth Steel syndrome Osteochondrodysplasia with hip

dislocations; dislocations of radial heads; carpal coalition; short stature; facial dysmorphism; scoliosis Cartilage oligomeric matrix protein (COMP) Cartilage, tendon, ligament, bone Pseudoachondroplasia Short-limb dwarfism; early-onset osteoarthritis Multiple epiphyseal dysplasia Mildly short stature; early-onset osteoarthritis Elastin Dermis, arterial wall, lung Cutis laxa Wrinkled, redundant, sagging inelastic skin Williams syndrome Cardiovascular disease (especially supravalvular aortic stenosis); orofacial features; intellectual deficit; connective tissue abnormalities; endocrine abnormalities Fibrillin 1 Dermis, arterial wall, lung Marfan syndrome Aortic root aneurysm or dissection; ectopia lentis; marfanoid habitus Weill-Marchesani-syndrome Short stature; joint stiffness; lens abnormalities; cardiovascular features Stiff skin syndrome Progressive rock-hard skin; flexion contractures; hypertrichosis Geleophysic dysplasia Short stature; joint stiffness; thickened skin; progressive cardiac valvular disease; orofacial features Fibrillin 2 Bruch membrane Congenital contractural arachnodactyly (CCA) or Beals-Hecht syndrome Acromelic dysplasia Relative short stature; brachydactyly; toe walking; early onset carpal tunnel syndrome; short palpebral fissures Fibronectin Dermis, tendons, ligaments Glomerulopathy with fibronectin deposits Glomerulopathy with fibronectin deposits Spondylometaphyseal dysplasia, corner fracture type

Heritable Disorders of Connective Tissue CHAPTER 425 Muscle weakness; joint contractures; joint hypermobility Tall stature; arachnodactyly; (kypho)scoliosis; pectus deformities; contractures; muscle hypoplasia; mild cardiovascular involvement; long, narrow face, highly arched palate, micrognathia, crumpled external ears Spondylometaphyseal dysplasia characterized by flake-like, triangular, or curvilinear ossification centers at the edges of irregular metaphyses that simulate fractures; short stature (Continued)

TABLE 425-1 Constituents of Connective Tissues and Their Associated Heritable Conditions PROTEIN TISSUE DISTRIBUTION DISEASE KEY MANIFESTATIONS Aggrecan Cartilage Spondyloepiphyseal dysplasia, Kimberley type Short stature; advanced bone age, with or without early-onset osteoarthritis and/or osteochondritis dissecans Spondyloepimetaphyseal dysplasia, aggrecan type Decorin Dermis, tendons, ligaments, cornea Congenital stromal corneal dystrophy Corneal stromal opacification; visual loss; increased corneal thickness PART 12 Endocrinology and Metabolism Biglycan Bone, cartilage, tendons Meester-Loeys syndrome Aortic aneurysm or dissection; orofacial features; joint hypermobility; ventricular dilatation on brain imaging; relative macrocephaly; hip dislocation; platyspondyly; phalangeal dysplasia; dysplastic epiphyses of the long bones X-linked spondyloepimetaphyseal dysplasia Abbreviation: EDS, Ehlers-Danlos syndromes. articular cartilage collagen. Glucocorticoids weaken most tissues by decreasing collagen synthesis. In some pathologic states, however, col lagen is deposited in excess. With most injuries to tissues, inflamma tory and immune responses stimulate the deposition of collagen fibrils in the form of fibrotic scars. In humans, as distinct from many other species, the deposition of the fibrils is largely irreversible and prevents regeneration of normal tissues in diseases such as hepatic cirrhosis, pulmonary fibrosis, atherosclerosis, and nephrosclerosis. Structure and Biosynthesis of Fibrillar Collagens The tensile strength of collagen fibers derives primarily from the self-assembly of protein monomers into large fibril structures in a process that resem bles crystallization. The self-assembly requires monomers of highly uniform and relatively rigid structure. It also requires a complex series of posttranslational processing steps that maintain the solubility of the monomers until they are transported to the appropriate extracellular sites for fibril assembly. Because of the stringent requirements for cor rect self-assembly, it is not surprising that

mutations in genes for fibril lar collagens cause many of the heritable diseases of connective tissues. The monomers of the three fibrillar collagens are formed from three polypeptide chains, called α chains, that are wrapped around each other into a rope-like triple-helical conformation. The triple helix is a unique structure among proteins, and it provides rigidity to the molecule. It also orients the side chains of amino acids in an “inside out” manner relative to most other proteins so that the charged and hydrophobic residues on the surface can direct self-assembly of the monomers into fibrils. The triple-helical conformation of the monomer is generated because each of the α chains has a repetitive amino acid sequence in which glycine (Gly) appears as every third amino acid. Each α chain contains ~1000 amino acids. Therefore, the sequence of each α chain can be designated as (-Gly-X-Y-)n, where X and Y represent amino acids other than glycine and n is >338. The presence of glycine, the smallest amino acid, in every third position in the sequence is critical because this residue must fit into a sterically restricted space in the interior of the helix where the three chains come together. The requirement for a glycine residue at every third position explains the significant clinical effects of mutations that convert a glycine residue to an amino acid with a bulkier side chain (see below). Many of the X- and Y-position amino acids are proline and hydroxyproline, which, because of their ring structures, provide additional rigidity to the triple helix. Other X- and Y-positions are occupied by charged or hydrophobic amino acids that precisely direct lateral and longitudinal assembly of the monomers into highly ordered fibrils. Mutations that substitute amino acids in some X- and Y-positions, particularly arginine-to-cysteine substitutions, can also produce genetic diseases. The fibers formed by the three fibrillar collagens differ in thick ness and length, but they have a similar fine structure. As viewed by electron microscopy, they all have a characteristic pattern of crossstriations that are about one-quarter the length of the monomers and

(Continued) Short stature; habitus; progressive osteoarthropathy; spondyloepiphyseal dysplasia Short stature and advanced bone age, with or without early-onset osteoarthritis and/or osteochondritis dissecans Severe short stature; spondyloepimetaphyseal dysplasia Severe short-trunked dwarfism; brachydactyly; spondyloepimetaphyseal dysplasia reflect the precise packing into fibrils. The three fibrillar collagens, however, differ in sequences found in the X- and Y-positions of the α chains and therefore in some of their physical properties. Type I col lagen is a heterotrimer, composed of two identical α1(I) chains and a third α2(I) chain that differs slightly in its amino acid sequence. Types II and III collagen are homotrimers, each composed of three identical α chains distinct to that type of collagen. To deliver a monomer of the correct structure to the appropriate site of fibril assembly, the biosynthesis of fibrillar collagens involves a large number of unique processing steps (Fig. 425-1). The monomer, first synthesized as a soluble precursor called procollagen, contains an additional globular domain at each end. As the pre-proα chains of pro collagen are synthesized on ribosomes, the free N-terminal ends move into the cisternae of the rough endoplasmic reticulum (ER). Signal peptides at the N-termini are cleaved, and additional posttranslational reactions begin. Proline and lysine residues in the Y-position of the Gly-X-Y repeating triplet are hydroxylated along the length of the helix by the enzymes prolyl 4-hydroxylase (P4H1) and lysyl hydroxylase (LH1), respectively. Hydroxyproline residues are essential for the three α chains of the monomer to fold into a triple helix at body tempera ture. P4H1 requires ascorbic acid as an essential cofactor, an observa tion that explains why wounds fail to heal in scurvy (Chap. 344). In scurvy, some of the underhydroxylated and unfolded protein accumu lates in the cisternae of the rough ER and is degraded. Many hydroxy lysine residues are glycosylated with galactose or with galactose and glucose. Also, a large mannose-rich

oligosaccharide is assembled on the C-terminal propeptide of each chain. The proα chains are assembled by interactions among these C-terminal propeptides that control the selection of the appropriate partner chains to form hetero- or homotrimers and provide the correct chain registration required for subsequent formation of the collagen triple helix. After the C-terminal propeptides assemble the three proα chains, a nucleus of triple helix is formed near the C-terminus, and the helical conformation is propa gated toward the N-terminus in a zipper-like manner that resembles crystallization. The folding into the triple helix is spontaneous in solu tion, but as discussed below, identification of rare mutations causing OI demonstrated that the folding in cellulo is assisted by a number of ancillary proteins that also prevent collagen fibril formation within the ER. The fully folded procollagen is then transported to the Golgi via a specific COPII vesicle process. After further modifications in the Golgi stack, the procollagen is secreted into the pericellular space where distinct proteases remove the N- and C-propeptides at specific cleavage sites. The release of the propeptides decreases the solubility of the resulting collagen ~1000-fold. The entropic energy that is released drives the self-assembly of the collagen into fibrils. Self-assembled collagen fibers have considerable tensile strength, but their strength is increased further by cross-linking reactions that form covalent bonds between α chains in one molecule and α chains in adjacent molecules.

Endoplasmic reticulum Late transport vesicles and extracellular matrix Polypeptide synthesis OH OH OH OH Collagen prolyl 4-hydroxylase Lysyl hydroxylase Prolyl 3-hydroxylase Collagen gal-transferase and glc-transferase OH OH OH OH O-Gal OH OH OH OH OH OH OH OH OH O-Gal-Glc -Gal-Glc OH Glc Gal O OH N glycosylated residue (Man)n GlcNAc SH OH OH OH Assembly of three procollagen chains OH OH OH SH SH OH OH SH O Gal Glc Gal O OH (Man)n GlcNAc OH OH OH S OH OH OH S S Protein disulfide isomerase OH OH S O Gal Assembly of triple helix Secretion of procollagen in transport vesicles FIGURE 425-1 Schematic summary of biosynthesis of fibrillar collagens. (Reproduced with permission from J Myllyharju, KI Kivirikko: Collagens, modifying enzymes and their mutations in humans, flies and worms. Trends Genet 20:33, 2004.) The resulting fibers, composed of hundreds or thousands of triplehelical monomers, have some of the properties of a crystal but have innate imperfections that make them highly flexible. Although the assembly of collagen monomers into fibers is largely a spontaneous reaction, the process in tissues is modulated by the pres ence of less abundant collagens (type V with type I, and type XI with type II) and by other components such as a series of small leucine-rich proteins (SLRPs). Some of the less abundant components alter the rate of fibril assembly, whereas others change the morphology of the fibers or their interactions with cells and other molecules. The presence of these other components is one explanation for why, in some tissues, the fibers are further assembled into large tendons; in others, into sheets; and in still others, into complex structures such as the hexago nal array of fibers that provide both the strength and transparency of the cornea. Collagen fibers are resistant to most proteases, but during degrada tion of connective tissues, they are cleaved by specific matrix metal loproteinases (collagenases) that cause partial unfolding of the triple helices into gelatin-like structures that are further degraded by less specific proteinases. ■ ■OTHER COLLAGENS AND RELATED MOLECULES The unique properties of the triple helix are used to define a family of at least 28 collagens that contain repetitive -Gly-X-Y- sequences and form triple helices of varying length and complexity. The proteins are heterogeneous both in structure and function, and many are the sites of mutations causing genetic diseases. For example, the type IV col lagen found in basement membranes is composed of three α chains synthesized from any of six different genes. Mutations in the COL4A3, COL4A4, or COL4A5 genes cause AS, while mutations in COL4A1

and rarely COL4A2 are associated with a spectrum of phenotypes including small-vessel brain disease of varying severity including porencephaly, variably associated with eye defects (retinal arterial tortuosity, Axen feld-Rieger anomaly, cataract) and systemic findings (kidney involve ment, muscle cramps, cerebral aneurysms, Raynaud phenomenon, cardiac arrhythmia, and hemolytic anemia).

N and C proteinases Heritable Disorders of Connective Tissue CHAPTER 425 Cleavage of propeptides Assembly into collagen fibrils Lysyl oxidase Formation of covalent cross-links Fibrillin Aggregates and Elastin In addition to tensile strength, many tissues such as the lung, large blood vessels, and ligaments require elasticity. The elasticity was originally ascribed to an amor phous rubber-like protein named elastin. Subsequent analyses, largely sparked by discoveries of mutations causing the Marfan syndrome (MFS), demonstrated that the elasticity resided in thin fibrils com posed primarily of large glycoproteins named fibrillins. The fibrillins contain large numbers of epidermal growth factor–like domains inter spersed with characteristic cysteine-rich domains that are also found in latent transforming growth factor β (TGF-β) binding proteins. The fibrillins assemble into long beadlike strands that also contain numer ous other components including small and variable amounts of elas tin, bone morphogenic proteins (BMPs), and microfibril-associated glycoproteins (MAGPs). Besides contributing to extracellular matrix structure, a major role for fibrillins in TGF-β signaling was empha sized by the discovery of mutations in genes coding for proteins involved in canonical TGF-β signaling in patients with Marfan-like manifestations, including thoracic aortic aneurysm. Proteoglycans The resiliency to compression of connective tis sues such as cartilage or the aorta is largely explained by the presence of proteoglycans. Proteoglycans are composed of a core protein to which are attached a large series of negatively charged polymers of disaccharides (largely chondroitin sulfates). At least 30 proteoglycans have been identified. They vary in their binding to collagens and other components of matrix, but specific functions have not been assigned to most. The major proteoglycan of cartilage, called aggrecan, has a core protein of 2000 amino acids that is decorated with ~100 side chains of chondroitin sulfate and keratin sulfate. The core protein, in turn, binds to long chains of the polymeric disaccharide hyaluronan to form proteoglycan aggregates, one of the largest soluble macromo lecular structures in nature. Because of its highly negative charge and extended structure, the proteoglycan aggregate binds large amounts of water and small ions to distend the three-dimensional arcade of col lagen fibers found in the same tissues. It thereby makes the cartilage resilient to pressure.

SPECIFIC DISORDERS

■ ■OSTEOGENESIS IMPERFECTA OI is a phenotypically and genetically heterogeneous generalized con nective tissue disorder. The hallmark features of OI are increased sus ceptibility to skeletal fractures, bone deformity, and growth deficiency. Bone fragility is based on decreased bone mass and increased bone brittleness due to defective mineralization. Secondary features of OI are highly variable even within a type and include blue sclerae, den tinogenesis imperfecta, hearing loss, basilar invagination, pulmonary function impairment, cardiac valve abnormalities, and ligamentous laxity. Most patients have defects in the structure or quantity of type I collagen. PART 12 Endocrinology and Metabolism Classification OI was originally classified into congenita and tarda subtypes depending on the age of symptom onset. Sillence proposed the classification that bears his name for four types based on clinical and radiologic findings and mode of inheritance. The

extension of the Sillence classification was first based on distinctive bone histol ogy (types V and VI OI) and subsequently on the discovery of new recessive genes (types VII–XXII). The debate between classification by phenotypic severity or gene defects has resulted in clinical and genetic classifications. The clinical classification can be useful for management but results in different type assignments in the same family or even in the same individual over their lifetime. The genetic classification (Table 425-2) groups patients by the causative gene. Because related causative genes were discovered close in time to each other, the genetic classification consequently groups types by overall mechanism and features OI as a collagen-related disorder. Types I–IV OI are due to quantitative or structural defects in type I collagen itself. Type I is the mildest subtype, with reduced quantity of structurally normal collagen, and can produce mild or inapparent skeletal deformities. Most patients have distinctly blue sclerae. Types II, III, and IV are all caused by structural defects in one of the type I col lagen α chains. Type II produces bone so brittle that infants have in utero fractures of ribs and long bones and die in the perinatal period. Type III is progressively deforming with moderate to severe bone deformity, and type IV has mild to moderate bone fragility and second ary features. Subsequent rare recessive OI types are all collagen-related. Types V and VI (ITITM5 and SERPINF1) particularly compromise matrix mineralization. Types VII, VIII, and IX (CRTAP, P3H1, and PPIB) represent defects in the components of the procollagen prolyl 3-hydroxylation complex that modifies collagen posttranslationally. Types X–XII and XXI (SERPINH1, FKBP10, BMP1, and KDELR1) have compromised procollagen processing and cross-linking. The final grouping of types XIII–XVIII (SP7, TMEM38B, WNT1, CREBL1, SPARC, MBTPS2, TEMTSA, MESD, CCDS134) alter osteoblast differ entiation and impair collagen matrix quality. The clinical heterogeneity of affected individuals within a particu lar OI type and even with the same mutation is not understood, with unknown modifying factors presumably involved. Among adults with OI, women are prone to fracture during pregnancy and after meno pause. Some variants of mild OI are first detected perimenopausally and must be distinguished from postmenopausal osteoporosis. Incidence In North America and Europe, the estimated incidence of OI is 1 per 10,000–15,000 births, based on a combination of cases recognized at birth and population surveys for milder cases. In popu lations with a high level of consanguinity or a founder mutation, the incidence of the rare recessive forms of OI is a significant addition to the prevalence of dominant collagen defects. Effects on Tissue Systems The phenotypic features of OI are highly variable, even within the types caused by defects in type I colla gen. The following section generally focuses on dominant forms com prising the majority of cases, except as specified, but the descriptions can be generalized to a large extent. Musculoskeletal Effects Bone in OI is both weak and brittle. At the mildest end of the spectrum (type I OI), individuals may have only several childhood fractures and be limited only from contact sports.

More severe forms of OI require bone to be partially unloaded with assistive devices such as walkers or canes; many severe patients use electric chairs for both the weight bearing and the normal speed of mobility. In dominant OI, fragility fractures often decrease sharply after adequate bone mass is gained at puberty. Radiographs generally show osteopenia in all types, with disordered matrix organization detected most easily in lower long bones in moderate and severe forms. In lethal OI, radiographs show continuous beading of ribs from healing fractures and crumpled and undertubulated long bones. Lateral skull radiographs may show islands of Wormian bones, even in mild forms. The appearance of “popcorn” at the metaphyses of long bones occurs in many type III and IV children and coincides with increased growth deficiency. Often these bones are so soft that normal muscle pull can produce severe deformities. Kyphoscoliosis is associated

with vertebral compressions but is not prevented by bisphosphonates, suggesting a contribution from ligamentous laxity. OI bone is weak, in that it fractures with a lower load than normal, and brittle, in that it does not tolerate postyield displacement and snaps like chalk. The brittleness results from the paradoxical increased min eralization of OI bone. While dual-energy x-ray absorptiometry (DXA) bone density measurements uniformly return a reduced value for OI bone, it is performed with a phantom and detects mineral crystals that are in proper alignment. In contrast, quantitative backscattered electron imaging or three-dimensional (3D) computed tomography (CT), which detect all mineral in 3D, reveals that both dominant and recessive (except types XIV and XV) OI bone is hypermineralized. On histomorphometry, dominant OI bone has proper formation of lamel lae but increased turnover, causing decreased bone volume. Type V OI has mesh-like bone lamellae, as well as a dislocated radial head, and may have hyperplastic callus formation, while type VI OI has distinc tive fish scale lamellae on polarized light microscopy. Many OI patients across the severity spectrum have increased ligamentous laxity. Patients with defects in processing the N-terminal propeptide of type I procollagen have large and small joint hypermobil ity similar to EDS. Muscle weakness of unknown etiology also occurs in OI, and the weakness and ligamentous laxity contribute to delayed motor development. Pulmonary The leading cause of death in OI is pulmonary disease. Young children with severe OI often have repeated pneumonia; restric tive or obstructive disease develops in most older children and adults. Pulmonary function is impaired by marked scoliosis and chest wall deformity but also arises from intrinsic defects of lung parenchyma containing type I collagen, as shown by declining pulmonary function over time in children without scoliosis. More recent studies have rein forced the significant role of intrinsic lung abnormalities in OI, dem onstrating reduced gas exchange, reduced airflow in small airways, and atelectasis in most individuals with collagen structural abnormalities. Bronchial thickening at the level of subsegmental bronchi in almost all patients further indicates the critical role of small airways. Mice with null CRTAP mutations (type VII OI) have abnormal alveolar develop ment, and patients with recessive forms also have pulmonary complica tions. Evaluation of even asymptomatic moderate to severe OI patients by spirometry should initiate standard pulmonary interventions. Cardiovascular Cardiovascular effects of OI manifest predomi nantly in adults. With type I collagen as a major component of matrix in cardiac valves and aortic wall, the most frequent manifestations are valvular, especially mitral regurgitation and aortic root dilatation. Impaired mechanical properties occasionally lead to aortic dissection. Echocardiography is appropriate with heart murmurs or cardiac symp toms and every 3–5 years in asymptomatic patients. Dentinogenesis Imperfecta Dentinogenesis imperfecta (DI) is associated with types III and IV OI and recessive types with collagen processing defects. Tooth agenesis, especially of premolars, is also found in types III/IV OI. Teeth with disturbed formation of dentin dur ing development may be translucent gray or have yellowish or brown ish discoloration. Defects are manifest predominantly in primary teeth; detection in secondary teeth may require radiographs to identify

defects V AD IFITM5 BRIL (BRIL5’ MALEP)

11p15.5 Yes Calcification of interosseous membrane, dense metaphyseal band, hyperplastic Atypical VI AD IFITM5 BRIL (BRIL Ser40Leu) 610967 11p15.5 Yes Increased osteoid, fish scale pattern in lamellar bone, increased ALP levels in modification VII AR CRTAP CRTAP

3q22.3 Yes Absent procollagen prolyl 3-hydroxylation; full OM, rhizomelia, white sclerae scoliosis; overlaps AD defects in type I collagen C-propeptide cleavage site VIII AR LERPE1 P3H1

1p34.2 Yes Absent procollagen prolyl 3-hydroxylation; full OM, rhizomelia, “popcorn” XII AR BMP1 BMP1

8p21.3 Yes Deficiency of C-propeptidase; skeletal deformity severe plus rhizomelia, VI AR SERPINF1 PEDF

17p13.3 Yes PEDF deficiency, increased osteoid, fish scale pattern in lamellar bone, 7q21.3 Yes Defects in 90 residues at N-terminus of collagen helix that decrease HBM AD COL1A1, COL1A2 Collagen α1 or α2 NA 17q21.33 Yes Defects in C-propeptide cleavage site, DXA normal to increased increased ALP levels in childhood, onset after age 1 year 7q21.3 Yes Structural defects in collagen helix or C-propeptides I AD COL1A1 Collagen α1

17q21.33 Yes Loss of function of one of the COL1A1 alleles callus, mesh-like pattern in lamellar bone childhood, symptom onset at birth GENE PROTEIN OMIM LOCUS HYPERMINERALIZATION DISTINGUISHING FEATURES pN-processing 259420, 166220 17q21.33, processing defects OI/EDS AD COL1A1, COL1A2 Procollagen α1 or α2 NA 17q21.33, II–IV AD COL1A1, COL1A2 Collagen α1 or α2 166210, TABLE 425-2 Different Types of Osteogenesis Imperfecta (OI) OI TYPE INHERITANCE DEFECTIVE Bone mineralization Defects in collagen Defects in collagen structure and Procollagen processing

MESD

15q25.1 ND Progressive deforming OI; severe to lethal; survivors have dental disorganization XVI AR CREB3L1 OASIS

11p11.2 Yes Defect in RIP pathway; Oasis substrate of S1P/S2P; severe skeletal fragility and Abbreviations: AD, autosomal dominant; ALP, alkaline phosphatase; AR, autosomal recessive; BMP, bone morphogenetic protein; DI, dentinogenesis imperfect; DXA, dual-energy x-ray absorptiometry; EDS, Ehlers-Danlos syndrome; HBM, X AR SERPINH1 HSP47

11q13.5 ND Severe skeletal deformity, blue sclerae, DI, skin abnormalities, inguinal hernias disorders XIX AR TEMT5A FAM46A

6q14.1 ND Defect in BMP/TGF-β signaling pathway; poly-adenylates transcripts of type I

7p22.1 ND Short stature, progressive skeletal deformation; dysmorphic facies, failure to XIV AR TMEM38B TRIC-B

9q31.2 No Decreased modification of collagen helix; Bedouin founder mutation; normal collagen, SERPINF1, and SPARC; severe to lethal OI; hyperlaxity, motor delay IX AR PPIB CyPB

15q22.31 Yes Absent procollagen prolyl 3-hydroxylation; helix modification varies, without

22q13.2 ND Severe OI with pseudoarthrosis; could also be classified with MAPK/ERK XVIII XR MBTPS2 S2P

Xp22.12 Yes X-linked OI, defect in RIP pathway; moderate to severe fragility, bowing; and intellectual disability; also classified with LRP5/6-related disorders XV AD/AR WNT1 WNT1

12q13.12 No AR cases have severe progressive OI; may have neurologic defects and differentiation XIII AR SP7 OSTERIX

12q13.13 ND Severe skeletal deformity, delayed tooth eruption, facial hypoplasia XVII AR SPARC SPARC

5q33.1 Yes Progressive severe bone fragility; hypotonia, joint laxity Heritable Disorders of Connective Tissue CHAPTER 425 thrive, hypotonia, joint hypermobility XI AR FKBP10 FKBP65

17q21.2 Yes May have congenital contractures high bone mass; NA, not applicable; ND, not determined; OI, osteogenesis imperfecta; OM, overmodification; OMIM, Online Mendelian Inheritance in Man; TGF, transforming growth factor. NA AR PLOD2 LH2

3q24 Yes Progressive joint contractures metaphyses; white sclerae rhizomelia, white sclerae skeletal dysplasias teeth, hearing rhizomelia deformity interacts with HSP47 XXII AR CCDC134 Coiled-coil domainretention receptor; containing protein XXI AR KDELR2 KDEL ER protein XX AR MESD LRP chaperone

Osteoblast function Defects in collagen Unclassified cross-linking folding and

characteristic narrow or obliterated pulp chambers. Crumbling at the dentin-enamel junction may require capping of teeth. Hypoplastic maxilla and relative mandibular prognathism in moderate to severe OI can result in type III malocclusion and impair normal chewing, requir ing surgical correction.

Hearing Loss About half of patients with types I, III, and IV OI develop hearing loss, but its incidence in recessive types is unknown. Hearing loss usually begins in the second decade and progresses. The initial conductive loss, based on changes in the inner ear leading to stapes footplate fixation, can evolve into a mixed conductive and senso rineural loss. Regular screening allows referral for hearing aids, stapes surgery, or cochlear implants, as appropriate. PART 12 Endocrinology and Metabolism Other Features A variable intensity of blue or grayish sclerae is a well-known feature of OI. The color is most striking with collagen defects, especially types I and II OI and defects that affect N-terminal procollagen processing. Blue sclerae often occur in other connective tissue disorders such as EDS or MFS and may occur in individu als without connective tissue defects. Severe neonatal OI with white sclerae should prompt consideration of recessive forms, especially prolyl 3-hydroxylation defects. Abnormalities of the skull base, such as platybasia and basilar invagination, sometimes progress to clini cally devasting basilar impression. Patients with height Z-scores of <–3 should be CT scanned at 3- to 5-year intervals. Significant growth deficiency is a cardinal feature of OI, ranging from minimally shorter than siblings in mild forms to greater extents in some severe cases, with adults shorter than 5-year-old children. There is both end-organ resis tance to growth hormone (GH) and defective transition to bone at the growth plate. Types I and IV OI are often responsive to recombinant GH therapy. Molecular Defects The great majority (80–85%) of cases of OI are caused by heterozygous mutations in either of the genes coding for the chains of type I procollagen, COL1A1 or COL1A2 (Table 425-2). Although thousands of unique mutations

have been identified in type I collagen, they fall into several structural types. Null mutations in collagen chains are less detrimental than structural defects. Null mutations in COL1A1 result in about half the normal level of collagen synthesis, but the collagen in matrix is structurally normal. These patients have mild type I OI. Null COL1A2 mutations are rare, leading to an EDS-like condition with progressive cardiac-valvular defects when present in homozygous state. Mutations that produce structural changes in type I collagen α chains cause types II, III, and IV OI. The most common of these are mutations resulting in substitutions for glycine residues required at every third residue along the helix. In effect, any of the 338 glycine residues in the helical domain of either the proα1 or proα2 chain of type I procollagen is a potential site for a disease-producing muta tion. Other mutations affect the splicing of the exons encoding the α chains. Because each collagen exon encodes a discrete set of Gly-X-Y triplets, the abnormal splice products are most often in-frame and cause severe structural abnormalities. Use of alternative splice sites may lead to premature termination, mimicking null mutations, and a milder phenotype. Structural abnormalities in the procollagen helical region delay collagen folding and expose chains to posttranslational hydroxylation/glycosylation for a longer time. The abnormal procolla gen triggers a cascade of intracellular and extracellular events including delayed collagen folding, ER stress, abnormal interaction with noncol lagenous molecules, impaired osteoblast development and cross-talk with osteoclasts, and abnormal mineralization. There are some special sets of procollagen structural mutations with distinct mechanisms within types II, III, and IV. Mutations in the C-propeptide significantly delay chain assembly, and resulting procollagen is mislocalized to the ER lumen. Some of this procollagen is targeted for degradation by the ER-associated proteosomal pathway, while the secreted molecules delay pericellular processing of the C-propeptide. Mutations in the C-propeptide cleavage site itself prevent processing of the propeptide, leaving pC-collagen to be incorporated into matrix. This affects matrix mineralization, resulting in an unusual high bone mass form of OI that

falls at the milder end of the type IV OI phenotype. Not surprisingly, null mutations in the C-propeptidase enzyme, BMP1, cause recessive type XII OI. Type XII OI is a severe condition because BMP1 is the cleavase for types I, II, and III procollagens and the glycoprotein deco rin, which is a regulator of fibrillogenesis. Processing defects of the N-propeptide occur in the cleavage site itself or the 90 helix residues at the amino end. The persistence of the N-propeptide on a fraction of the molecules interferes with the self-assembly of normal collagen so that thin and irregular collagen fibrils are formed. They cause extreme laxity of large and small joints, intensely blue sclerae, and an OI sever ity comparable to type III/IV. Rare substitutions of charged amino acids (Asp, Arg) or a branched amino acid (Val) in X- or Y-positions produce lethal phenotypes, apparently because they are located at sites for lateral assembly of the monomers or binding of other components of the matrix. Starting in 2006, a series of noncollagenous genes have been identi fied that cause (mostly) recessive OI. Importantly, all the genes have encoded proteins or cellular processes related to collagen, shifting the OI paradigm to dominant OI caused by collagen defects or IFITM5 and recessive OI caused by proteins related to collagen modification, processing, folding, and cross-linking and osteoblast differentiation. The largest group of patients with OI not caused by collagen gene mutations have types V and VI OI, affecting bone mineralization. Type V OI, with dominant inheritance, is unusual in that all patients have the same recurrent mutation at the 5′-end of IFITM5, which generates a novel start codon in the transmembrane protein BRIL. The gain-of-function mutation causes distinctive radiologic (ossifi cation of interosseus membrane and dense metaphyseal band) and phenotypic findings (hypertrophic callus). Osteoblasts with type V OI have

increased mineralization and differentiation in culture. Type VI OI is a recessive form caused by null mutations in PEDF, a collageninteracting molecule with a known antiangiogenic effect. A connection between types V and VI OI has been revealed by a set of patients with a BRIL p.S42L substitution who have clinical, histologic, serum marker, and phenotypic features of type VI OI. Both type VI OI osteoblasts and BRIL p.S42L osteoblasts have decreased cellular mineralization and SERPINF1 expression, while classic type V OI osteoblasts have the opposite findings. All three types decrease collagen production. Types VII, VIII, and IX OI are severe recessive forms caused by deficiency of one of the components of the procollagen prolyl 3-hydroxylation complex, P3H1, CRTAP, or cyclophilin B (PPIB/ CyPB). This complex 3-hydroxylates one proline residue per α chain, most critically α1(I)P986, in contrast to the proline 4-hydroxylation of multiple helical residues by P4H1. In murine models, loss of complex function results in a severe phenotype, while mutation of the P986 residue impairs collagen cross-linking and fine-tuning of collagen alignment in fibrils. The phenotype of these patients is distinctive for white sclerae, rhizomelia, and lack of relative macrocephaly; they share the bone fragility, high bone turnover, and elevated bone mineraliza tion of classical OI. Some recessive OI types that impair osteoblast function are caused by mutation in genes not previously understood to affect bone. Regu latory intramembrane proteolysis (RIP) is well known for its role in cholesterol synthesis, in which cells transport regulatory proteins from the ER membrane to the Golgi membrane in times of cell stress, where S1P and S2P Golgi proteases sequentially cleave the transcription fac tors, activating them to enter the nucleus. X-linked type XVIII OI with defective MBTPS2/S2P and type XVI OI with deficiency of an RIP sub strate Oasis, a member of the ATF6 family of stress sensors, indicate the importance of RIP for bone formation (Table 425-2). For more recently identified OI types, the relationship of the causative gene to collagen has extended the spectrum of matrix abnormality. FAM46A (type XIX OI) polyadenylates collagen transcripts; defects lead to collagen defi ciency approaching a null COL1A1 allele that does not fully explain the severe disorganization of collagen in bone matrix. Since FAM46A also polyadenylates the transcripts of other OI-causative genes, SERPINF1 and SPARC, the matrix defect may be multifactorial. For type XX OI, MESD is a direct cytosolic chaperone of pro-alpha1(I) chains, but several bone features that are not typical of OI, such as oligodontia and

cartilage remnants, may reflect MESD’s role as a chaperone for LRP5. KDELR2 defects (OI type XXI) have impaired retrograde transport of ER resident proteins, such as HSP47, because KDELR2 is a compo nent of CopI vesicles. Collagen quantity in matrix is lower because of reduced collagen expression, but the impaired collagen fibrillogenesis may be caused by increased interaction of HSP47 with collagen mono mers in the extracellular space. The causative gene for type XXII OI, CCDC134, is involved in the MAPK signaling pathway. The osteoblasts of affected individuals have increased ERK1/2 phosphorylation as well as reduced COL1A1 and osteopontin expression. Inheritance and Mosaicism in Germline Cells and Somatic Cells Types I–V OI are inherited as autosomal dominant traits, while the rare forms are mostly recessive. Many patients with mild dominant OI represent familial traits, while sporadic new mutations are often responsible for dominant severe or lethal cases. Germline mosaicism in one parent may be the etiology of a severe dominant mutation in the child; in this circumstance, a second child may be affected with the same dominant mutation from unaffected parents. Recessive mutations in genes causing the rare forms of OI lead to more severe clinical outcomes; many of these offspring do not survive child hood, but moderately to severely affected young adults show us that these conditions must also be considered. Diagnosis OI is usually diagnosed on the basis of clinical and radiographic criteria. The presence of fractures together with blue sclerae, DI, or family history of the disease is usually

sufficient to make the diagnosis. X-rays reveal a decrease in bone density that can be veri fied by DXA bone densitometry, as well as characteristic deformities of long bones, thorax, and cranium. The differential diagnosis varies with age, including battered child syndrome, nutritional deficiencies, malignancies, and other inherited disorders such as chondrodysplasias and hypophosphatasia that can have overlapping presentations. A molecular diagnosis is now routinely obtained using targeted candidate gene sequencing, sometimes beginning with the dominant collagen and IFITM5 panel. Skeletal disorder gene panels and whole-exome sequencing may be financially advantageous and pick up additional skeletal gene variants as well as the OI-causative gene. Although almost all cases can be diagnosed by sequencing, some may require bone his tology and exome sequencing. TREATMENT Osteogenesis Imperfecta Therapy should be directed toward maximizing the function of each individual, which includes decreasing fractures and deformity that interfere with function. Physical and occupational therapy are critical modalities. They are most commonly utilized after severe fractures or major surgery and should also be engaged consistently throughout the life span for maximizing mobility, functions of daily living, and the extent of physical conditioning possible. Water ther apy is particularly useful at all ages. Diet should include adequate intake of calcium and vitamin D. Many patients are underweight for height as young children but overweight as adults, and nutritional management may be useful. Orthopedic procedures are required for deformities of long bone that interfere with standing or walking or when a bone has sustained repeated fractures. Intramedullary rods are often inserted when children are ready to stand and as needed thereafter to keep bone segments in good alignment and provide partial unloading of weight from bones. If scoliosis progresses, sta bilization of the spine may be needed to maintain the curve at <60°. Medical management should also include presymptomatic screen ing for hearing loss, cardiac valve dysfunction, pulmonary function, and, in severe individuals, basilar invagination. Drugs that have been developed for the therapy of postmeno pausal osteoporosis are beneficial for some patients. Bisphospho nates, antiresorptive drugs that inhibit osteoclasts, increase DXA bone density and relieve vertebral compressions in most patients. They are regarded as a mainstay of care in many pediatric centers.

However, several Cochran reports have not supported a clear reduction in fracture rate or bone pain from their use, and the dos ing and duration of use are controversial. Currently, drugs with a bone-forming mechanism are in trials for OI, especially monoclo nal antibodies to sclerostin that relieve its inhibition of osteoblast Wnt/β-catenin signaling, TGF-β inhibitors, and a PTH analogue that stimulates osteoblasts and is most beneficial for adults with milder OI. Potential therapies under investigation in animal models include chemical chaperones and mesenchymal stem cell therapy, and, currently in murine models, correction of specific defects in collagen by CRISPR. Heritable Disorders of Connective Tissue CHAPTER 425 ■ ■EHLERS-DANLOS SYNDROMES The Ehlers-Danlos syndromes (EDS) comprise a genetically heteroge neous group of heritable conditions that share several characteristics such as soft and hyperextensible skin, abnormal wound healing, easy bruising, and joint hypermobility. Additional clinical features that dif fer among the EDS types include fragility of soft tissues, blood vessels, and hollow organs and involvement of the musculoskeletal system and the eye. Mutations in genes coding for fibrillar collagens (type I, III, or V) are found in many patients, but other genes are affected in rare forms. Classification Several types of EDS have been defined, based on clinical characteristics, mode of inheritance, and molecular defects (Table 425-3), and the classification of these types has been a dynamic process. The current classification defines 13 clinical EDS types that are caused by alterations in 19 different genes, but a recent study described another genetically distinct EDS

type, bringing the total number of EDS-associated genes to 20. The EDS classification guides the clinical diagnosis, molecular confirmation, and genetic counseling of affected individuals and their family members. Incidence An incidence of about 1 in 5000 individuals for all forms of EDS was proposed, with no apparent ethnic predisposition. The diagnosis of hypermobile EDS is more common in females than in males, but whether this is due to an increased incidence or more severe manifestation is unknown. The incidence for other types of EDS is similar in males and females. With incidences of 1 in 20,000 and 1 in 50,000–200,000 respectively, classic and vascular EDS are the most common genetically elucidated types of EDS. For the other types of EDS for which causative variants have been identified, there are no incidence estimates, but the numbers of people who have been reported worldwide with these disorders range between ~5 and ~100 individuals per EDS type. Patients with milder forms frequently do not seek medical attention. Skin One of the principal features of EDS is skin hyperextensibility, that is, the skin stretches easily but snaps back after release. The skin often has a smooth, soft, or velvety feel to it and can be thin and trans lucent. It is fragile and tears easily, even after minor trauma, and heals slowly. Widened and thin atrophic scars are frequently observed in different types of EDS. Especially in classic EDS, atrophic scarring may be widespread, especially over pressure points and exposed areas such as the forehead, elbows, knees, and shins, with marked widening of the scars, which are covered by a very thin inelastic skin (papyraceous scars). Individuals with vascular EDS usually do not have a velvety hyperextensible skin, but skin can be thin and translucent with visible superficial veins. Easy bruising is common to most types of EDS and may manifest itself as spontaneous or recurring hematomas. These may cause discoloration of the skin due to deposition of hemosiderin, often referred to as “hemosiderotic” scars, especially in classic, vascular, and periodontic EDS. Ligament and Joint Changes Joint hypermobility, another cardi nal sign, is variable in severity and usually, but not always, generalized. While often an “asset” in childhood, it can become a serious burden over time, often complicated by repetitive subluxations, dislocations, sprains, and chronic joint pain that is difficult to treat. Other observed musculoskeletal features include congenital bilateral hip dislocation,

Spontaneous sigmoid colon perforation in the absence of known colon Severe generalized joint hypermobility with multiple dislocations Carotid-cavernous sinus fistula (in the absence of trauma) Progressively redundant, lax skin with excessive skinfolds Dermatosparactic EDS (dEDS) AR

5q35.3 ADAMTS2 ADAMTS2 Extreme skin fragility with congenital or postnatal tears Uterine rupture during third trimester of pregnancy Proα2(V) Skin hyperextensibility with atrophic scarring Classic EDS (cEDS) AD / 17q21.33 COL1A1 Proα1(I) p.Arg312Cys Skin hyperextensibility with atrophic scarring PART 12 Endocrinology and Metabolism Proα2(I) Congenital bilateral hip dislocation Generalized joint hypermobility Generalized joint hypermobility Arterial rupture at young age Vascular EDS (vEDS) AD

2q32.2 COL3A1 Proα1(III) Arterial rupture at young age Increased palmar wrinkling EDS TYPE INHERITANCE OMIM LOCUS GENE PROTEIN KEY MANIFESTATIONS Skin hyperextensibility Craniofacial features Severe bruisability Umbilical hernia disease COL5A2 Proα1(V) COL1A2 Proα1(I) 2q32.2 COL5A1 7q21.3 COL1A1

17q21.33

9q34.3 Classic EDS (cEDS) AD

Arthrochalasia EDS (aEDS) AD

TABLE 425-3 Different Types of Ehlers-Danlos Syndrome (EDS) Defects in collagen primary structure and collagen processing

Classic-like EDS type 1 (clEDS1) AR

6p21.33-p21.32 TNXB Tenascin XB Skin hyperextensibility with velvety skin texture and absence of atrophic Myopathic EDS (mEDS) AD/AR

6q13-q14 COL12A1 Proα1(XII) Congenital muscle hypotonia and/or muscle atrophy Generalized joint hypermobility with (sub)luxations Cardiac-valvular EDS (cvEDS) AR

7q21.3 COL1A2 proα2(I) Severe progressive cardiac-valvular insufficiency Perinatal complications related to tissue fragility Easily bruisable skin/spontaneous ecchymoses Postnatal growth retardation with short limbs Congenital or early-onset kyphoscoliosis Generalized joint hypermobility FKBP22 Congenital muscle hypotonia Joint hypermobility Joint hypermobility Joint contractures Skin involvement scarring FKBP14 Lysylhydroxylase 1 7p14.3 PLOD1

1p36.22 AR

AR collagen cross-linking Kyphoscoliotic EDS (kEDS-PLOD1) Kyphoscoliotic EDS (kEDS-FKBP14) Defects in collagen folding and interface between muscle and function of myomatrix, the Defects in structure and ECM

sulfotransferase-1 Congenital multiple contractures (typically adduction/flexion contractures Skin hyperextensibility, easy bruising, skin fragility with atrophic scars Muscle hypotonia (ranging from severe congenital to mild later-onset) Muscle hypotonia (ranging from severe congenital to mild later-onset) C1s Severe and intractable early-onset periodontitis β4GalT7 Short stature (progressive in childhood) (spEDS-SLC39A13) AR

11p11.2 SLC39A13 ZIP13 Short stature (progressive in childhood) Increased palmar wrinkling and talipes equinovarus) Lack of attached gingiva Craniofacial features Skeletal dysplasia Skeletal dysplasia Pretibial plaques Bowing of limbs Bowing of limbs (spEDS-B3GALT6) AR

1p36.33 B3GALT6 Galactosyltransferase II (spEDS-B4GALT7) AR

5q35.3 B4GALT7 Galactosyltransferase I (mcEDS-DSE) AR

6q22.1 DSE Dermatan sulfate epimerase-1 (mcEDS-CHST14) AR

15q15.1 CHST14 Dermatan-4 β3GalT6 C1S C1r pathways Periodontal EDS (pEDS) AD

12p13.31 C1R Musculocontractural EDS Musculocontractural EDS biosynthesis Spondylodysplastic EDS Spondylodysplastic EDS processes Spondylodysplastic EDS Defects in glycosaminoglycan

Defects in complement Defects in intracellular

Exclusion of other EDS types and other joint hypermobility-associated Systemic manifestations of generalized connective tissue fragility Early-onset progressive keratoconus and/or keratoglobus Unclassified Classic-like EDS type 2 (clEDS2) AR

7p13 AEBP1 AEBP1 (ACLP) Skin hyperextensibility with atrophic scarring Heritable Disorders of Connective Tissue CHAPTER 425 PRDM5 Thin cornea with/without rupture Generalized joint hypermobility Unknown Hypermobile EDS (hEDS) ? (AD)

? ? ? Generalized joint hypermobility Musculoskeletal complaints Early-onset osteopenia Positive family history Foot deformities Blue sclerae conditions PRDM5 ZNF469 Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ECM, extracellular matrix; OMIM, Online Mendelian Inheritance in Man. 4q27 ZNF469

16q24 Brittle cornea syndrome (BCS) AR

spine deformities (scoliosis, kyphosis), pectus deformities (pectus carinatum, pectus excavatum), club feet and other contractures, and in some rare types, a (mild) skeletal dysplasia. Muscle hypotonia is observed in a number of EDS types and, in combination with joint lax ity, may cause floppy infant syndrome or a delay in motor development.

Other Features Signs of more generalized connective tissue weak ness and fragility can be observed in varying degrees and may help to distinguish between the different EDS types. Rupture of medium and large-sized arteries is typical of vascular EDS but has been reported in a few other types as well, i.e., classic and kyphoscoliotic type. Vascular EDS patients are also at increased risk for rupture of the gastrointes tinal tract, especially the sigmoid colon, the gravid uterus, and, more rarely, other internal organs such as liver or spleen. Valvular defects and aortic root dilatation are rare and are also restricted to some of the rarer types of EDS. Obstetrical and pelvic complications such as cervi cal insufficiency, premature rupture of membranes, vaginal lacerations, and organ prolapses (uterus, bladder, rectum) may occur. Sclerae may be blue, and more severe ophthalmologic complications, including keratoconus, keratoglobus, and scleral or corneal rupture, may be observed in some rare types. PART 12 Endocrinology and Metabolism Molecular Defects Subsets of patients with different types of EDS have mutations in the structural genes for fibrillar collagen types I, III, and V (Table 425-3). About 90% of classic EDS patients harbor a heterozygous mutation in COL5A1 or COL5A2 cod ing for type V collagen, a minor collagen found in association with type I collagen. Heterozygous mutations in the COL3A1 gene for type III collagen, which is abundant in the blood vessel wall, are responsible for vascular EDS. Arthrochalasia EDS is caused by hetero zygous mutations in either COL1A1 or COL1A2 that make type I pro collagen resistant to cleavage by the procollagen N-proteinase ADAMTS2, whereas dermatosparaxis EDS is caused by biallelic muta tions in the gene that codes for the ADAMTS2 itself, thereby reducing its enzyme activity. The persistence of the N-propeptide causes the formation of collagen fibrils that are thin and irregular. Other specific mutations in either COL1A1 or COL1A2 give rise to a few rare types of EDS. These include the cardiac-valvular type, which is caused by bial lelic COL1A2 mutations, leading to a complete absence of α2(I) chains. Patients with this condition are at risk for severe, progressive cardiacvalvular disease necessitating valve replacement. A specific arginineto-cysteine

substitution in the type I collagen α chain (p.Arg312Cys) is associated with an EDS phenotype that resembles that of classic EDS, but patients appear at increased risk for vascular rupture of mediumsized arteries. A few patients with a phenotype that couples EDS with signs of moderate to severe myopathy harbor heterozygous or homozy gous mutations in COL12A1, coding for type XII collagen, a fibrilassociated collagen with interrupted triple helices. Kyphoscoliotic EDS is caused by biallelic mutations either in the PLOD1 gene, which encodes procollagen-lysine 5-dioxygenase (lysyl hydroxylase 1), an enzyme required for formation of stable cross-links in collagen fibers, or in the FKBP14 gene, which encodes FKBP22, an endoplasmic resi dent molecular chaperone that acts as a quality control on the folded triple helix of type III collagen. Some patients with clinical character istics that resemble those of classic EDS harbor biallelic mutations in either TNXB, encoding tenascin X, an extracellular matrix glycoprotein that appears to regulate the assembly of collagen fibers, or in AEBP1, which encodes the extracellular matrix–associated adipocyte enhancer-binding protein (AEBP1), which assists in collagen polymer ization. Spondylodysplastic EDS is caused by biallelic mutations in B3GALT7, coding for galactosyltransferase I, or in B3GALT6, coding for galactosyltransferase II, both key enzymes in the biosynthesis of the linker region of glycosaminoglycans. Musculocontractural EDS results from mutations in genes coding enzymes responsible for dermatan biosynthesis: CHST14, dermatan 4-O-sulfotransferase 1, and DSE, der matan sulfate epimerase. A rare spondylodysplastic type of EDS is caused by biallelic mutations in SLC39A13, encoding the intracellular zinc transporter ZIP13. Brittle cornea syndrome is caused by biallelic mutations in either ZNF469 or PRDM5, both (putative) transcriptional

regulators. Finally, periodontal EDS is caused by heterozygous muta tions in C1R or C1S, coding for the complement pathway components C1q and C1s, respectively. Diagnosis Diagnostic workup comprises clinical examination and should be followed by genetic testing in individuals who are suspected to have an EDS type. Genetic testing can include targeted mutation analysis in those with a family history of EDS caused by a known genetic variant or, more frequently, next-generation sequencing using multigene panels. Genetic diagnosis should lead to family testing. Of note, the genetic cause of hypermobile EDS has not been determined, and therefore, diagnosis of this condition is based on the presence of clinical manifestations and the exclusion of other types of EDS or other conditions associated with joint hypermobility. Correlations between genotype and phenotype are challenging and only starting to emerge, and as with other heritable diseases of connective tissue, there is a large degree of variability among members of the same family carrying the same mutation. TREATMENT Ehlers-Danlos Syndrome All patients with EDS should receive multidisciplinary care and, if available, be part of a patient advocacy community. The precise treatment depends on the type of EDS and the clinical manifesta tions. Physiotherapy is essential for patients with musculoskeletal problems. Helmets and/or skin protections or joint protections, braces, or splints can be used to reduce the risk of injury in patients with skin fragility or joint hypermobility. Low-resistance exercises (such as walking or swimming) can improve joint stability, although exercises that place considerable strain on the joints (such as gym nastics or weightlifting) should be avoided. Monitoring for cardio vascular alterations using noninvasive procedures is recommended in patients at risk of adverse cardiovascular events only. Given the rarity of vascular EDS, referral to a center with EDS expertise is of vital importance. A clear protocol for emergency room evalua tion in the case of major complications should be established, and patients should carry documentation of their genetic diagnosis, such as a MedicAlert. The psychosocial impact of a vascular EDS diagnosis often requires psychological care. ■ ■CHONDRODYSPLASIAS (See also Chap. 424) Chondrodysplasias (CDs), also referred to as skeletal

dysplasias or osteochondrodysplasias, encompass a heteroge neous group of disorders characterized by intrinsic abnormalities of cartilage and bone and are generally characterized by dwarfism and abnormal body proportions (disproportionate short stature). Many affected individuals develop degenerative joint changes, and mild CD in adults may be difficult to differentiate from primary generalized OA. Classification The Nosology and Classification of Genetic Skeletal Disorders comprises 771 distinct disorders based on clinical, radio graphic, and/or molecular phenotypes. Pathogenic variants have cur rently been found in 551 different genes. The conditions are divided into 41 groups based on gene/protein families (e.g., the type II collagen group), phenotypic presentation (e.g., spondylometaphyseal dysplasia), and pathophysiology (i.e., lysosomal storage disorders). One gene may be responsible for more than one condition (e.g., COL2A1 mutations may cause a number of CDs including achondrogenesis, hypochondro genesis, spondyloepiphyseal dysplasia congenita, Kniest and Stickler syndromes), or a condition may be due to mutations in more than one gene (e.g., geleophysic dysplasia can be caused by mutations in ADAMTSL2, FBN1, and LTBP3). Incidence The overall incidence of all forms of CD ranges from 1 per 2500 to 1 per 4000 births. Data on the frequency of individual CDs are incomplete. The most common form of inherited disproportionate short stature is achondroplasia, with an estimated incidence of 1 per 26,000 to 1 per 28,000 live births.

Molecular Defects Mutations in the COL2A1 gene, coding for the α chain of type II collagen of cartilage, are found in a group of patients with both mild and severe CDs. For example, a mutation in COL2A1 substituting a cysteine residue for an arginine was found in a few unrelated families with spondyloepiphyseal dysplasia (SED) and precocious generalized OA. Mutations in the gene were also found in some lethal CDs characterized by gross deformities of bones and cartilage, such as those found in SED congenita, spondyloepime taphyseal dysplasia congenita, hypochondrogenesis/achondrogenesis type II, and Kniest syndrome. The highest incidence of COL2A1 muta tions, however, occurs in patients with the distinctive features of the Stickler syndrome, which is characterized by skeletal changes, orofacial abnormalities, and ophthalmologic and auditory abnormalities. Most of the mutations in COL2A1 are premature stop codons that produce haploinsufficiency. In addition, some of the patients with Stickler syn drome or a closely related syndrome have mutations in two genes specific for type XI collagen (COL11A1 and COL11A2), which is an unusual heterotrimer formed from α chains encoded by COL2A1, COL11A1, and COL11A2. Mutations in the COL11A1 gene are also found in patients with Marshall syndrome, which is similar to classic Stickler syndrome, but with more severe hearing loss and dysmorphic features, such as a flat or retracted midface with a flat nasal bridge, short nose, anteverted nos trils, long philtrum, and large-appearing eyes. CDs are also caused by mutations in the less abundant collagens found in cartilage. For example, patients with Schmid metaphyseal CD have mutations in the gene for type X collagen, a short, networkforming collagen found in the hypertrophic zone of endochondral cartilage. The syndrome is characterized by short stature, coxa vara, flaring metaphyses, and waddling gait. As with other collagen genes, the most common mutations are of two types: nonsense mutations that lead to haploinsufficiency and structural mutations that compromise collagen assembly. Some patients have mutations in genes for proteins that interact with collagens. Patients with pseudoachondroplasia or autosomal dominant multiple epiphyseal dysplasia have mutations in the gene for the carti lage oligomeric matrix protein (COMP), a protein that interacts with both collagens and proteoglycans in cartilage. However, some families with multiple epiphyseal dysplasia have a defect in one of the three genes for type IX collagen (COL9A1, COL9A2, and COL9A3) or in matrilin-3, another extracellular protein found in

cartilage. Some CDs are caused by mutations in genes that affect early development of cartilage and related structures. Achondroplasia is caused by mutations in the gene for a receptor for a fibroblastic growth factor (FGFR3). The mutations in the FGFR3 gene causing achondroplasia are unusual in several respects. More than 99% of individuals with achondroplasia have one of two pathogenic variants (c.1138G> or c.1138G>C) in FGFR3, both resulting in the amino acid change p.Gly380Arg. Most patients harbor a sporadic new (de novo) mutation, and therefore, this nucleotide change is one of the most common recurring mutations in the human genome. The muta tion causes unregulated signal transduction through the receptor and inappropriate development of cartilage. Mutations that alter other domains of FGFR3 have been found in patients with the more severe disorders of hypochondroplasia and thanatophoric dysplasia and in a few families with a variant of craniosynostosis. However, most patients with craniosynostosis appear to have mutations in the related FGFR2 gene. The similarities between the phenotypes produced by mutations in genes for fibroblast growth factor (FGF) receptors and mutations in structural proteins of cartilage are probably explained by the observa tion that the activity of FGFs is regulated in part by binding of FGFs to proteins sequestered in the extracellular matrix. Therefore, the situ ation parallels the interactions between transforming growth factors (TGFs) and fibrillin in MFS (see below). Other mutations involve the proteoglycans of cartilage, aggrecan (AGC1) and perlecan (HSPG2), and in the proteoglycan posttransla tional sulphation pathway (DTDST, PAPSS2, and CHST3). Diagnosis The diagnosis of CDs is made on the basis of the physi cal appearance, slit-lamp eye examinations, x-ray findings, histologic

changes, and clinical course. Targeted gene and exome sequencing or more global sequencing strategies are used for molecular diagnosis. Given the wide spectrum of CD phenotypes, these genetic tests are becoming critical diagnostic tools. For Stickler syndrome, more precise diagnostic criteria have made it possible to identify type I variants with mutations in the COL2A1 gene with a high degree of accuracy. It has been suggested that the type II variant with mutations in the COL11A1 gene can be identified on the basis of a “beaded” vitreous phenotype and that the type III variant with mutations in the COL11A2 gene can be identified on the basis of the characteristic systemic features without the ocular involvement. Prenatal diagnosis based on analysis of DNA obtained from chorionic villus or amniotic fluid is possible.

Heritable Disorders of Connective Tissue CHAPTER 425 TREATMENT Chondrodysplasias The treatment of CDs is symptomatic and is directed to secondary features such as degenerative arthritis. Many patients require joint replacement surgery and corrective surgery for cleft palate. The eyes should be monitored carefully for the development of cataracts and the need for laser therapy to prevent retinal detachment. In general, patients should be advised to avoid obesity and contact sports. Counseling for the psychological problems of short stature is critical. A randomized, double-blind, phase 3, placebo-controlled, multicenter trial with vosoritide, a biologic analogue of C-type natriuretic peptide, which is a potent stimulator of endochondral ossification, in children with achondroplasia showed that this is an effective and safe treatment to increase growth in children with achondroplasia. ■ ■HERITABLE THORACIC AORTIC

ANEURYSM DISEASE Heritable thoracic aortic aneurysm disease (HTAD) encompasses conditions in which aortic disease has a familial occurrence, due to an underlying genetic defect. HTAD is classified as syndromic or nonsyn dromic. Syndromic HTAD may be associated with ocular, craniofacial, musculoskeletal, and skin features, with a recognizable, yet sometime subtle,

phenotype. They are caused by mutations in genes that code for extracellular matrix proteins. Besides syndromic HTAD, there are several nonsyndromic forms of HTAD; patients with these conditions do not display an outward recognizable phenotype and are classified as having familial thoracic aortic aneurysm (FTAA). More extensive genetic screening in cohorts of patients with thoracic aortic aneurysm is, however, slowly revealing that there is no strict boundary between syndromic and nonsyndromic HTAD entities (Table 425-4) (Chap. 291). Classification The most common form of syndromic HTAD is MFS, caused by mutations in the gene for fibrillin-1 (FBN1). MFS was initially characterized by a triad of features: (1) skeletal changes that include long, thin extremities, frequently associated with loose joints; (2) reduced vision as the result of dislocations of the lenses (ectopia lentis); and (3) aortic aneurysms. An international panel has developed a series of revised Ghent criteria that are useful in clas sifying patients. Other major syndromic HTADs include the different genetic variants of Loeys-Dietz syndrome (LDS) (TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD2, and SMAD3). Rare forms of syndromic HTAD include Shprintzen-Goldberg syndrome (SKI), Meester-Loeys syndrome (BGN), and arterial tortuosity syndrome (ATS) (SLC2A10). Incidence and Inheritance The incidence of MFS is among the highest of any heritable disorder: ~1 in 3000–5000 births in most racial and ethnic groups. The related syndromes are less common. Muta tions are generally inherited as autosomal dominant traits, but about one-fourth of patients have sporadic new mutations. The LDSs are less common, but their exact incidence is currently unknown. Skeletal Effects Patients with MFS typically display a marfanoid habitus with tall stature and long limbs. The ratio of the upper segment (top of the head to the top of the pubic ramus) to the lower segment

TABLE 425-4 Heritable Thoracic Aortic Disease and Associated Genes and Proteins GENE PROTEIN CONDITION OMIM LOCUS Extracellular matrix proteins COL3A1 α1(III) collagen chain Vascular EDS

2q32 FBN1 Fibrillin 1 Marfan syndrome

15q21.1 MFAP5 Microfibrillar associated protein 5 Familial thoracic aortic aneurysm 9

12p13.31 LOX Lysyl oxidase Familial thoracic aortic aneurysm 10

5q23.1 TGF-β signaling TGFBR1 Transforming growth factor receptor 1 Loeys-Dietz syndrome 1

9q22.33 TGFBR2 Transforming growth factor receptor 2 Loeys-Dietz syndrome 2

3p24.1 SMAD3 Mothers against decapentaplegic drosophila homolog 3 Loeys-Dietz syndrome 3

15q22.33 TGFB2 Transforming growth factor β2 Loeys-Dietz syndrome 4

1q41 PART 12 Endocrinology and Metabolism TGFB3 Transforming growth factor β3 Loeys-Dietz syndrome 5

14q23.3 SMAD2 Mothers against decapentaplegic drosophila homolog 2 Arterial aneurysms and dissections / 18q21.1 ACTA2 Smooth muscle actin α2 Familial thoracic aortic aneurysm 6

10q23.31 Smooth muscle contraction MYH11 Smooth muscle myosin heavy chain 11 Familial thoracic aortic aneurysm 4

16p13.11 MYLK Myosin light chain kinase Familial thoracic aortic aneurysm 7

3q21.1 PRKG1 Protein kinase cGMP-dependent type 1 Familial thoracic aortic aneurysm 8

10q11.2-q21.1 Abbreviations: EDS, Ehlers-Danlos syndromes; OMIM, Online Mendelian Inheritance in Man; TGF, transforming growth factor. (top of the pubic ramus to the floor) is usually 2 standard deviations below mean for age, race, and sex. The fingers and hands are long and slender and have a spider-like appearance (arachnodactyly). Overlap ping features in MFS and LDS include scoliosis or kyphoscoliosis; anterior chest deformities, including pectus excavatum, pectus carina tum, or asymmetry; pes planus; pneumothorax; and dural ectasia. A few patients have severe joint hypermobility similar to EDS. Clubfeet, joint contractures, and cervical spine instability are more frequently observed in LDS. Patients with SMAD3 mutations are particularly prone to premature OA. Cardiovascular Features Cardiovascular abnormalities are the major source of morbidity and mortality both in MFS and LDS (Chap. 291). Patients with MFS often have mitral valve prolapse that develops early in life and that progresses to mitral valve regurgitation of increasing severity in about one-quarter of patients. Dilation of the root of the aorta and the sinuses of Valsalva are characteristic and omi nous features of MFS that can develop at any age. The rate of dilation is unpredictable, but it can lead to aortic regurgitation, dissection of the aorta, and rupture. Dilation is probably accelerated by physical and emo tional stress as well as by pregnancy. Cardiovascular features of LDS also include dilatation of the aortic root at the level of the sinus of Valsalva, which can progress to dissection or rupture when left untreated. LDS is also known for its involvement of aneurysms affecting arterial branches of head, neck, thoracic and abdominal aorta, lung, and lower extremities and for the presence or tortuosity of these vessels. In contrast to MFS, congenital heart malformations are often noted. Ocular Features Myopia is the most common ocular feature of MFS and often presents in early childhood. Displacement of the lens from the center of the pupil (ectopia lentis) occurs in ~60% of MFS patients. The ocular globe is frequently elongated. Retinal detachment, early cataract formation, and glaucoma can occur. Ectopia lentis does not usually occur in LDS, but other ocular features may be present, such as blue sclerae, strabismus, amblyopia, and myopia. Other Features MFS patients typically have a high arched palate. Patients with LDS characteristically display hypertelorism (widely spaced eyes) and cleft palate or bifid (split) uvula. They may also have craniosynostosis. Shared mucocutaneous features include striae, typi cally over the shoulders and buttocks, and inguinal and incisional her nias. Patients with LDS may display more EDS-like skin features, such as thin translucent skin and widened scars. Molecular Defects Approximately 95% of MFS patients are explained by FBN1 defects, and so far, over 2000 different FBN1 mutations have been described. Mutations in the same gene are found in a few patients who do not meet the Ghent criteria. Most FBN1 gene mutations are unique and are scattered throughout its 65 coding

exons. Approximately 10% are recurrent mutations that are largely located in CpG sequences known to be “hot spots.” About one-third of the mutations introduce premature termination codons, and about two-thirds are missense mutations that alter calcium-binding domains in the repetitive epidermal growth factor–like domains of the protein. Rarer mutations alter the processing of the protein. As in many genetic diseases, the severity of the phenotype cannot be predicted from the nature of the mutation. In LDS, components of the TGF-β signaling pathway are mutated, including the cytokines (TGFβ2, TGFβ3), the receptors (TGFBR1, TGFBR2), and the downstream effectors (SMAD2, SMAD3). The discovery that various conditions with pronounced clinical overlap with MFS were caused by mutations in genes coding for direct effectors and/or

regulators of TGFβ signaling, including LDS, revealed that FBN1 mutations not only lead to weakening of the extracellular matrix structure, but also influence the bioavailability of TGFβ. As a result, some of the manifestations of MFS have been shown to arise from alterations in binding sites that modulate TGFβ bioavailability during development of the skeleton and other tissues. In aortic tis sues, reduced or altered forms of fibrillin-1 can stimulate the release of sequestered TGFβ and increase its activity. This results in altered transcription of target genes, including connective tissue growth factor and matrix metalloproteinases MMP2 and MMP9. The aortic pheno type is therefore caused by vascular remodeling due to a combination of structural microfibril changes, excess TGFβ, and overexpression of MMP-2 and MMP-9. The role of TGFβ in the pathophysiology of MFS has been further solidified by therapeutic use of angiotensin 2 recep tor blockers (ARBs), proven to decrease TGFβ activity, to reduce the progression of aortic dilation. However, clinical trials with ARBs did not provide evidence of a dramatic decrease or prevention of aortic growth with ARBs. Diagnosis When HTAD is present, genetic testing can confirm the diagnosis and allow identification of at-risk individuals. Referral to a specialty genetics service is critically important, and genetic counsel ing before testing is recommended. In view of phenotypic overlap between the syndromic HTAD, a multigene panel (usually including genes for syndromic and nonsyndromic HTAD) is recommended. All patients with a suspected diagnosis of MFS should have a slit-lamp examination and an echocardiogram. Also, homocystinuria should be ruled out by amino acid analysis of plasma (Chap. 431). The diagnosis of MFS according to the international Ghent standards places empha sis on two cardinal features, dilation of the ascending aorta with or without dissection and ectopia lentis. Other cardiovascular and ocular manifestations and findings in other organ systems such as the skel eton, dura, skin, and lungs contribute to a systemic score that guides diagnosis when aortic disease is present but ectopia lentis is not.

Revision #1
Created 2026-01-06 16:35:29 UTC by Omar Ayman
Updated 2026-01-06 16:35:29 UTC by Omar Ayman