coding 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 are particularly vulnerable to a large number different mutations 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 hyperextensible skin, in some patients with dwarfism, and in patients with other disorders, including Alport's syndrome, that were not initially classified as disorders of connective tissue. Also, mutations in collagen genes were found in subset of patients with a diagnosis of osteoarthritis and a subset of patients with the diagnosis of osteoporosis. However, the search for mutations quickly expanded to hundreds of other genes that included those for other structural proteins, for the posttranslational processing of structural proteins, and for growth factors and their receptors, and other genes whose functions are still not fully understood.

In many instances, the mutations helped to define the clinical subtype of the disorder. In others, however, they did not. Some patients with the same clinical presentations were found to have mutations in different genes. Also, some patients with different manifestations were found to have mutations in the same genes. In addition, it was difficult to establish whether a change in the structure of a gene caused the phenotypic changes in patients and was not simply a neutral polymorphism. Therefore, there has been a continuing debate as to whether the disorders should be classified by their clinical presentations or by the genetic abnormalities. As an illustration of the problem, mutations in 226 genes have been found to be associated with the 456 defined disorders of the skeleton, but the latest nosology remains a "hybrid" between a list of clinically defined disorders, waiting for molecular clarification, and an annotated database documenting the phenotypic spectrum produced by mutations in a given gene. A simpler system of classification proved feasible for one rare heritable disorder of skin, epidermolysis bullosa. The disorder was first defined by the presence of friction-induced blister. It was then divided into subtypes that were defined by the ultrastructural layers of the skin that cleaved and blistered. Most patients in each subtype were subsequently shown to have mutations in genes expressed in the corresponding layer of skin. Even with these patients, however, the strength of the genotype-phenotype correlation varies, and mutations have not yet been found in every patient.

In the end, consensus reports by experts in the field and sources such as the Online Mendelian Inheritance in Man database provide valuable resources for physicians searching for diagnoses of patients with unusual clinical features. However, patients with the most common forms of the disorders have mutations in a limited number of genes. This chapter will focus primarily on these more common disorders.

COMPOSITION OF CONNECTIVE TISSUES

Connective tissues such as skin, bone, cartilage, ligaments, and tendons are the critical structural frameworks of the body important for development and function. They consist of a complex interacting extracellular matrix network of collagens, proteoglycans, and a large number of noncollagenous glycoproteins and proteins. Although these precise combinations of up to ~500 potential extracellular matrix building blocks 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 427-1). The most abundant components are three similar fibrillar collagens (types I, II, and III). They have a similar tensile

TABLE 427-1 CONSTITUENTS OF CONNECTIVE TISSUES

Connective Tissue	Major Constituents	Approximate Amounts, % dry wt	Characteristics or Functions
Dermis, ligaments, tendons	Type I collagen	80	Large bundles of fibrils
	Type III collagen	5–15	Thin fibrils
	Type IV collagen, laminins, and nidogen	<5	Form basal laminae under epithelium
	Types V, VI, and VII collagens	<5	V modifies type I fibrils; VI forms beaded microfibrils; VII forms anchoring fibrils for epidermis
	Fibrillin aggregates/elastin	<5	Provide elasticity
	Fibronectin	<5	Associated with collagen fibers and cell surfaces
	Proteoglycans[a]/hyaluronan	<0.5	Provide resiliency
Bone (demineralized)	Type I collagen	90	Complex fibril network
	Type VI collagen	1–2	Beaded microfibrils
	Proteoglycans[a]hyaluronan	1	Function unclear
	Osteonectin, osteopontin, osteocalcin, α2-glycoprotein, and sialoproteins	1–5	May regulate mineralization
Aorta	Type I collagen	20–40	Fibril network
	Type III collagen	20–40	Thin fibrils
	Fibrillin aggregates/elastin	20–40	Provide elasticity
	Type IV collagen, laminins, and nidogen	<5	Form basal lamina under endothelial cells
	Types V and VI collagens	<2	V modifies type I fibrils; VI forms beaded microfibrils
	Proteoglycans[a]/hyaluronan	<3	Provide resiliency
Cartilage	Type II collagen	40–50	Arcades of thin fibrils
	Type IX collagen	5–10	Links type II fibrils and other components
	Type VI collagen	<1	Beaded microfibrils, largely pericellular
	Type X collagen	5–10	Forms pericellular network in hypertrophic growth plate cartilage
	Type XI collagen	<10	Incorporated into some type II fibrils
	Proteoglycans[a]/hyaluronan	15–50	Provide resiliency
	Small leucine-rich repeat proteins (SLRPs; >6 kinds)	<5	Multiple functions in assembly and function of the tissue

[a]Over 30 proteoglycans have been identified. They differ in the structures of their core proteins and their contents of glycosaminoglycan side chains of chondroitin-4-sulfate, chondroitin-6-sulfate, dermatan sulfate, and keratin sulfate. Basal lamina contains a proteoglycan with a side chain of heparan sulfate that resembles heparin.