Hearing Loss Hearing loss usually begins during the second decade of life and occurs in more than 50% of individuals over age 30. The loss can be conductive, sensorineural, or mixed, and it varies in severity. The middle ear usually exhibits maldevelopment, deficient ossification, persistence of cartilage in areas that are normally ossified, and abnormal calcium deposits.

Other Features Changes in other connective tissues can include thin skin that scars extensively, joint laxity with permanent dislocations indistinguishable from those of Ehlers-Danlos syndrome (EDS), and occasionally, cardiovascular manifestations such as aortic regurgitation, floppy mitral valves, mitral incompetence, and fragility of large blood vessels. For unknown reasons, some patients develop bouts of a hypermetabolic state with elevated serum thyroxine levels, hyperthermia, and excessive sweating.

Molecular Defects Of the ~1360 unique gene mutations now described in OI, more than 90% are heterozygous mutations in either *COL1A1* or *COL1A2*, the genes coding for the proα1 or proα2 chain of type I procollagen (Table 427-2).

Most patients with type I OI and blue sclerae have mutations that reduce the synthesis of proα1 chains to about one-half. Mutations that reduce the synthesis of proα2 chains produce slightly more severe phenotypes and skin defects similar to EDS.

In contrast to the null mutations found in type I OI, most of the severe variants (types II, III, and IV) are caused by mutations that produce structurally abnormal proα chains that have compromised assembly or abnormal folding of the triple helix. As with collagen mutations in other connective tissue diseases, these structural mutations generally fall into two functional categories. First, the relatively rare mutations in the C-propeptide domain can prevent or seriously impair initial assembly of the procollagen trimers. These misfolded chains are retained in the endoplasmic reticulum (ER) and targeted for degradation by the ER-associated proteasomal pathway. Because these mutations induce an ER stress response, the unfolded protein response (UPR) may have many downstream effects on cells. ER stress is a new concept in the pathophysiology of connective tissue disease and has been best characterized for chondrodysplasias (see below).

The most common type I collagen mutations, however, are single base substitutions that introduce an amino acid with a bulky side chain for one of the glycine residues that appear as every third amino acid in the triple 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 mutation. These mutations compromise the structural integrity of the triple helix, causing disruption to helix folding, retention of the mutant trimers in the ER, and increased posttranslational hydroxylation and glycosylation of lysines. Collagen-containing helix mutations can form insoluble aggregates in the ER that are degraded by the autophagosome-endosome system, rather than the proteasomes.

A similar sequence of events occurs with less common mutations that produce partial gene deletions, partial gene duplications, and splicing mutations. In addition to their intracellular effects, the structurally abnormal mutant-containing collagen that is secreted by the cell can also have important extracellular affects. For example, the presence of one abnormal proα chain in a procollagen molecule can interfere with cleavage of the N-propeptide from the protein. 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. Furthermore, if structurally abnormal collagens are incorporated into fibrils, they may have a destabilizing effect and be selectively degraded, or they may alter the interactions of collagen with other connective tissue components, disturbing architecture and stability.

Several generalizations can be made about mutations in type I collagen genes. One is that unrelated patients rarely have the same mutation in the same gene. Glycine substitutions in the N-terminal region of the triple helix tend to produce milder phenotypes, apparently because they have less effect on the zipper-like propagation of the triple-helical conformation from the C terminus. 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.

The search for mutations causing the less common and autosomal recessive forms of OI identified mutations in genes for a series of proteins that are essential for the timely folding of the procollagen monomer: cartilage-associated protein (*CRTAP*), prolyl-3-hydroxylase (*LEPRE1*/P3H1), cyclophilin B (*PPIB*), collagen chaperone-like protein HSP47 (*SERPINH1*), and the procollagen chaperone protein FKBP65 (*FKBP10*). Recently, mutations have been characterized in additional downstream components of the collagen fibrillogenesis pathway: *BMP1*, the gene coding for a metalloproteinase that cleaves the C-propeptide of type I procollagen, and *PLOD2* (LH2, lysyl oxidase 2), which is involved in establishing collagen cross-links. In addition to these mutations that affect the collagen assembly pathway, mutations have been characterized in genes involved in the regulation of bone formation and mineralization such as *SP7* (osterix), *IFITM5*, *WNT1*, and *TMEM38B* (Table 427-2).

Inheritance and Mosaicism in Germline Cells and in Somatic Cells Type I OI is inherited as an autosomal dominant trait. However, some patients with type I OI appear to represent sporadic new mutations or a diagnosis that was missed in earlier generations. Most lethal OI is the result of sporadic mutations that occur in the germ line in one of the parents. Because of the possibility for germline mosaicism for newly generated mutations, there is about a 7% probability that a second child could inherit a severe variant of OI.

Diagnosis OI is usually diagnosed on the basis of clinical criteria. The presence of fractures together with blue sclerae, dentinogenesis imperfecta, or family history of the disease is usually sufficient to make the diagnosis. Other causes of pathologic fractures must be excluded, including battered child syndrome, nutritional deficiencies, malignancies, and other inherited disorders such as chondrodysplasias and hypophosphatasia that can have overlapping presentations. The absence of superficial bruises can be helpful in distinguishing OI from battered child syndrome. X-rays usually reveal a decrease in bone density that can be verified by photon or x-ray absorptiometry. Bone microscopy can be helpful in the diagnosis. The diagnosis, as in other genetic disorders, is now routinely determined using targeted candidate gene sequencing and exome sequencing, but whole-genome sequencing may be used in the future.

TREATMENT OSTEOGENESIS IMPERFECTA

Many patients with OI lead productive and successful lives despite severe deformities. Those with mild forms of the disease may need little treatment when fractures decrease after puberty, but women require special attention during pregnancy and after menopause, when fractures again increase. More severely affected children require a comprehensive program of physical therapy and surgical management of fractures and skeletal deformities.

Many fractures are only slightly displaced and have little soft tissue swelling and, therefore, can be treated with minimal support or traction for a week or two followed by a light cast. If fractures are relatively painless, physical therapy can be initiated early. A judicious amount of exercise prevents loss of bone mass secondary to physical inactivity. Some physicians advocate insertion of steel rods into long bones to correct limb deformities; the risk/benefits and cost/benefits of such procedures are difficult to evaluate. Aggressive conventional intervention is usually warranted for pneumonia and cor pulmonale. For severe hearing loss, stapedectomy or replacement of the stapes with a prosthesis may be successful. Moderately to severely affected patients should be evaluated periodically to anticipate possible neurologic problems. About half of children have a substantial increase in growth when given growth hormone. Treatment with bisphosphonates to decrease bone loss has been introduced for moderate to severe forms of OI. Improvements in bone mineral