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 413-2). 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.

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 mutation. 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 procollagen triggers a cascade of intracellular and extracellular events including delayed collagen folding, ER stress, abnormal interaction with noncollagenous 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