A N-terminal glycine to cysteine mutation in the collagen COL1A1 gene produces moderately severe osteogenesis imperfecta. (W. Wilcox, L. Scott, and D. Cohn.) Division of Medical Genetics, Cedars-Sinai Medical Center, Los Angeles, California.

Osteogenesis Imperfecta (OI) is usually due to mutations in the type I procollagen genes COL1A1 and COL1A2. Point mutations close to the N-terminus are generally milder than those near the C-terminus of the molecule (the gradient hypothesis of collagen mutations). We describe a patient with moderately severe OI due to a mutation in the N-terminal portion of the triple helical domain of the α1(I) chain. Electrophoretic analysis of collagen isolated from fibroblast cultures suggested the abnormal presence of a cysteine in the N-terminal portion of the α1(I) chain. Five overlapping DNA fragments amplified from fibroblast RNA were screened for mutations using single strand conformational polymorphism (SSCP) and heteroduplex analyses. Direct DNA sequence analysis of the single positive fragment demonstrated a G to T transversion, corresponding to a glycine to cysteine substitution at position 226 of the triple helical domain of the α1(I) chain. The mutation was confirmed by restriction enzyme analysis of amplified genomic DNA. The mutation was not present in fibroblasts from either phenotypically normal parent. Combining this mutation with other reported mutations, glycine to cysteine substitutions at positions 205, 211, 223, and 226 produce a moderately severe phenotype whereas flanking mutations at positions 175 and 382 produce a mild phenotype. This data supports a regional rather than a gradient model of the relationship between the nature and location of type I collagen mutations and OI phenotype.

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