

## OSTEOGENESIS IMPERFECTA - CLINICAL AND MOLECULAR DIVERSITY

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**INTRODUCTION:** Osteogenesis imperfecta (OI) is a heritable medical disorder characterized by bone fragility due to impairment in bone quantity and quality, which may present with a wide range of disease severity. The term osteogenesis imperfecta has been used to describe the clinical features of this disorder since the nineteenth century, long before any underlying gene mutations were described. Many individuals with OI are now known to possess mutations in one of the two genes for type I collagen (COL1A1 and COL1A2), though others do not. However, while OI exhibits both clinical and molecular diversity, it is not possible to clearly distinguish clinical phenotypes on the basis of their gene mutation.

**CLINICAL DIVERSITY:** The most widely used clinical classification of OI is that proposed by Sillence, which divides OI into four types. Type I OI describes individuals with the mildest form of the disease. Fractures are not common at birth, incidence remains low throughout life, and there is little skeletal deformity. Type II OI describes individuals with the most severe form of the disease, who die in utero or soon after birth. Multiple fractures are present in the fetal bones, which are severely deformed. Type III OI represents the most severe phenotype compatible with post-natal life. Individuals have multiple fractures and show severe and progressive skeletal deformity. Type IV OI encompasses those individuals who fall between the type I and III categories, and represents the most phenotypically heterogeneous group. It has now been recognized that type IV OI can be subdivided based on radiographic, histologic and metabolic characteristics and this has led to expansion of the classification system. Type V OI describes individuals who show distinctive hypertrophic callus formation at healing fracture sites and calcification of interosseous membranes in the forearm. Type VI OI describes individuals with signs of a bone mineralization defect, but in the absence of metabolic abnormalities associated with rickets/osteomalacia. Type VII OI describes individuals with characteristic rhizomelic shortening of the femur and humerus and a recessive inheritance. Other categories of OI undoubtedly exist and await formal identification.

**MOLECULAR DIVERSITY:** About 70% of all individuals who can be classified with OI possess a mutation in either their COL1A1 or COL1A2 gene. Those who do not possess such a mutation include all individuals with types V, VI and VII OI. These newer forms of OI are definitely not due to mutations in the genes encoding type I collagen. In the case of type VII OI, the existence of large pedigrees has enabled the

causative gene to be localized to chromosome 3p22-24.1, a region in which no collagen gene or osteoid protein gene has yet been described. The sporadic nature of types V and VI OI has so far precluded identification of the locus of the causative gene. The absence of any detectable COL1A1 or COL1A2 mutation also occurs in some individuals with classical types I, III and IV OI, albeit a minority of individuals. Of those individuals with a COL1A1 or COL1A2 mutation, the majority involve point mutations perturbing a glycine codon. In our experience such mutations represent about 80% of those detected in the COL2A1 gene, but 40% in the COL1A1 gene. The other mutations in the COL1A1 gene reflect deletions or insertions giving rise to a frameshift, point mutations at donor or acceptor sites involved in splicing, or point mutations generating a premature stop codon. The majority of individuals with these latter types of mutation have relatively mild disease. For the glycine mutations, disease severity shows regional variation in relation to the location or type of amino acid substitution, rather than showing discrete trends.

**DISCUSSION:** Because of the molecular heterogeneity of OI, disease diagnosis should be based on clinical presentation. This is particularly true at present, as current medical treatment of the disease is applicable to all forms of OI. Until specific gene therapy approaches are developed and accepted, medical intervention is aimed at increasing the quantity of bone by bisphosphonate therapy. This can lower fracture incidence, improve quality of life, and make orthopaedic intervention less problematic.

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