REVIEW ARTICLE

Osteogenesis imperfecta: new genes reveal novel mechanisms in bone dysplasia

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Osteogenesis imperfecta (OI) is a skeletal dysplasia characterized by fragile bones and short stature and known for its clinical and genetic heterogeneity which is now understood as a collagen-related disorder. During the last decade, research has made remarkable progress in identifying new OI-causing genes and beginning to understand the intertwined molecular and biochemical mechanisms of their gene products. Most cases of OI have dominant inheritance. Each new gene for recessive OI, and a recently identified gene for X-linked OI, has shed new light on its (often previously unsuspected) function in bone biology. Here, we summarize the literature that has contributed to our current understanding of the pathogenesis of OI (Translational Research 2016;■:1–21)

Abbreviations: ■ = ■■■

INTRODUCTION

Osteogenesis imperfecta (OI) is a heterogeneous group of rare genetic disorders of connective tissue. With its primary impact on bone, it is also known as "brittle bone disease." Typical clinical manifestations are bone fragility, low bone mass, skeletal deformities, and short stature. It is also a systemic disorder that involves extraskeletal structures. This encompasses various clinical manifestations, including dentinogenesis imperfecta, blue-gray sclera, hearing impairment, joint hypermobility, muscle hypotonia, restrictive pulmonary disease, and cardiovascular abnormalities. Overall, the prevalence of OI is estimated at 1 in 15,000–20,000 births. The severity of OI ranges from perinatal lethal and severely deforming types to very mild forms without deformity. Genetic heterogeneity of OI is further complicated by extensive phenotypic variability of each genetic locus and different modes of inheritance.

More than 80% of OI cases are due to dominantly inherited mutations in *COL1A1* or *COL1A2*, which encode the α1(I) and α2(I) chains of type I collagen.[1] With 2 exceptions (interferon-induced transmembrane protein 5 [*IFITM5*] and *WNT1*), mutations in noncollagen genes are associated with recessive forms of OI.[2] One recessive type is X-linked. Generally, homozygous or compound heterozygous loss-of-function mutations result in severely decreased or absent production of protein. Recessive OI genes can be generally categorized based on the cellular pathways in which their molecular functions are executed (Table I). Recessive OI genes that are involved in collagen biosynthesis, post-translational modification, and processing include cartilage-associated protein (*CRTAP*), *LEPRE1*, *PPIB*, *FKBP10*, *SERPINH1*, *PLOD2*, *TMEM38B*, and *BMP1*. The mutations in *SP7* and *WNT1* indicate the significance of osteoblast development and activity. Delineation of mutations in membrane-bound transcription factor peptidase site 2 (*MBTPS2*) and *CREB3L1* underscores the critical importance of regulated intramembrane proteolysis (RIP) in skeletal development. Improved understanding of osteoblast differentiation

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Table I. Overview of osteogenesis imperfecta types based on causative genes and function

OI type	Inheritance	Defective gene	Defective protein
Defects in collagen synthesis and structure			
Type I, II, III, IV	AD	*COL1A1* or *COL1A2*	α1(I) or α2(I) collagen
Defects in bone mineralization			
Type V	AD	*IFITM5*	BRIL
Type VI	AR	*SERPINF1*	PEDF
Defects in collagen modification			
Type VII	AR	*CRTAP*	CRTAP
Type VIII	AR	*LEPRE1*	P3H1
Type IX	AR	*PPIB*	PPIB (CyPB)
Defects in collagen processing and crosslink			
Type X	AR	*SERPINH1*	HSP47
Type XI	AR	*FKBP10*	FKBP65
Unclassified	AR	*PLOD2*	LH2
Type XII	AR	*BMP1*	BMP1
Defects in osteoblast differentiation and function			
Type XIII	AR	*SP7*	SP7 (OSTERIX)
Type XIV	AR	*TMEM38B*	TRIC-B
Type XV	AR/AD	*WNT1*	WNT1
Type XVI	AR	*CREB3L1*	OASIS
Type XVII	AR	*SPARC*	SPARC (Osteonectin)
Type XVIII	XR	*MBTPS2*	S2P

Abbreviations: AD, Autosomal dominant; *AR*, autosomal recessive; *XR*, X-linked recessive.

and bone matrix mineralization will be derived from studies of OI caused by mutations in *IFITM5* and *SERPINF1*. Overall, identification of new OI-causing genes has greatly extended the scope of cellular and biological pathways for OI pathogenesis. Here, we review the recent advances in mechanistic implications of those genes in OI pathogenesis.

Defects in collagen synthesis, structure, and processing. Type I procollagen, like other fibrillar collagens, is characterized by N- and C-terminal propeptide sequences flanking a central helical region containing uninterrupted Gly-X-Y repeats (where X and Y represent any amino acid but are frequently proline and hydroxyproline). In type I procollagen, 3 α-chains (2 α1 and 1 α2 chain) are assembled, beginning with chain assortment and alignment in the C-propeptide. The type I procollagen molecule undergoes post-translational modification in the endoplasmic reticulum (ER). Procollagen maturation requires the cleavage of the propeptides by specific N- and C-terminal propeptidases.

Mutations in the 2 type I collagen genes, *COL1A1* and *COL1A2*, cause autosomal dominant OI. The OI-causing mutations in type I collagen can be divided into quantitative defects, with the synthesis of structurally normal collagen at about half the normal amount, and structural defects, that result in synthesis and secretion of abnormal collagen molecules. The quantitative defects are generally caused by premature termination codons in 1 *COL1A1* allele, which initiate the nonsense-mediated decay of transcripts from that allele. The resulting matrix deficiency causes mild type I OI.[3-7]

Collagen structural mutations that alter the chain sequence in the triple helical domain result in a wide phenotypic range from lethal type II OI to moderate type IV OI. Most commonly, these mutations cause a substitution of one of the invariant glycine residues in the triple helical domain of α1(I) or α2(I) chains, because of the crucial role of glycine in helix formation.[8,9] Mutations in *COL1A1* that result in the substitution of glycine by serine, cysteine, and arginine account for 78.6% of all α1(I) substitutions. About one-third of all independent glycine substitutions in α1(I) result in perinatal lethal type II OI; especially, substitution by amino acids with charged or branched side chains. About a quarter of all *COL1A1* glycines at which substitutions have been identified now have 2 or more independent occurrences of substitutions; these residues are scattered along the length of the α1(I) chain and are often associated with CpG dinucleotides. Interestingly, recurrences at the same α1(I) glycine residue frequently have different clinical outcomes.[10]

Mutations in *COL1A2* that result in α2(I) glycine substitutions by serine, aspartic acid, and valine comprise about three-quarters of known independent events in the helical domain, although substitutions by arginine, valine, and alanine should predominate if mutations occur randomly in the first and second positions of the