Beyond brittle bones: Genetic mechanisms underlying osteogenesis imperfecta (Review)

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Abstract. Osteogenesis imperfecta (OI) is a heritable genetic disorder characterized by osteoporosis, severe bone fragility and reduced bone mineral density. It is mostly caused by mutations in genes, such as collagen type I alpha 1 chain (*COL1A1*) and collagen type I alpha 2 chain (*COL1A2*), which are responsible for synthesizing type I collagen. Of note, 90% of cases of OI are caused by dominantly inherited genes, such as *COL1A1* or *COL1A2*, while only 10% of cases are caused by 23 recessive genes. The present review summarizes the genes associated with different types of OI. The present review also highlights the importance of cyclical bisphosphonate treatment for patients with OI for improving bone mineral mass, mobility score, reducing the fracture rate and decreasing pain episodes. The aim of the present review was to provide insight into management policies for the disease, providing knowledge for clinicians/researchers in classifying the types of OI and to ultimately search for more effective therapeutic strategies. Furthermore, the present review provides information that may prove useful for improving patient management, diagnostic accuracy and treatment plans for patients affected by OI, with the aim of enhancing their prognosis.

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1. Introduction

Osteogenesis imperfecta (OI) or 'brittle bone disease' is a heritable genetic disorder characterized by severe bone fragility, osteoporosis and reduced bone mineral density (1,2). It is mostly caused by pathogenic mutations in the collagen type I alpha 1 chain (*COL1A1*) and collagen type I alpha 2 chain (*COL1A2*) genes, which are responsible for producing collagen type 1. However, defects in these genes negatively affect collagen in bones rather than in other organs of the body (3). It has been documented that 90% of cases of OI are caused by heterozygous mutations in *COL1A1* or *COL1A2*, inherited in autosomal dominant manner, while 10% of cases of OI are caused by 23 genes inherited in an autosomal recessive manner (Table I).

The hallmark of OI includes bone softness with fractures, with minimum to moderate physical injury. In severe cases of the disease, the fractures are observed at birth and involve both long bones of the upper and lower limbs. Femoral fractures are the most commonly observed and frequently cause phenotypic deformity. There is a flattening of the posterior skull with the protruding calvarium and a face with a triangular-shaped appearance (4). It is significant to note that the OI types are not classified solely based on severity. Rather, the severity of OI and its classification varies; for example, type I is more severe followed by type IV followed by type III, and then type II, respectively. Type V, type VI and type VII have a mild phenotypic presentation. Of note, the severity of OI is continuous (OI as continuous reflects the complexity and variability of the disorder, recognizing that it manifests differently in each individual and can change over time) and the disease has a high clinical heterogeneity. As new genes are reported frequently due to next-generation technologies, a new classification of OI is periodically required. Even within different types of

OI, there is immense clinical diversity in disease types. The degree of severity of manifestations, such as scoliosis, dentinogenesis imperfecta (DI) and bone softness can differ from one subject to another, even if both subjects have the same type of OI (Fig. 1) (5). The present review extends the classification of OI, which may aid researchers and clinicians in the proper diagnosis, management and treatment of OI cases.

2. Collagen

During bone formation, a specific type of collagen is assembled as procollagen, and amino (N) terminal and carboxy (C) terminal propeptides are then sliced. The main part of the molecule, a triple helix of collagen, is assimilated into the bone matrix. This specific type of collagen is known as type 1 collagen. Collagens include a large group of triple-helical proteins, which are the most plentiful protein in vertebrates, indicating 30% of the total proteins. There are 29 genetically different types of collagen known that are translated by 44 different genes (6). Based on molecular structure and assembly style, they can be categorized into different subgroups (7). The largest subgroups of collagen are types I, II, III, V, XI, XXIV and XXVII.

3. Prevalence and molecular diversity of OI

OI is a rare inherited brittle bone disorder with a different prevalence ratio recorded in different countries. The overall prevalence of the different types of OI is ~1/15,000 or 1/20,000 births and the majority of the cases are genetically caused by mutations in the *COL1A1* or *COL1A2* genes (8).

As regards the molecular diversity of OI, clinically and genetically, OI types are classified into various types. It is frequently discussed in an autosomal recessive, dominant and X-linked pattern (8,9). The novel extended classification of OI is very diverse with variability in severity, phenotypes and different inheritance patterns. Still, new genes are discovered, increasing the diversity of OI-related pathogenesis (3).

4. Classification of autosomal dominant OI

Type I OI (COL1A1: OMIM 166200). OI type I (MIM 166200) is the mildest form of OI and its characteristic features include fractures, hearing loss and blue sclera. Milder bone deformity has been noted in individuals with type I OI, such as progressive hearing loss, otosclerosis, blue sclerae, the heart having mitral valve prolapse deformity, mild osteopenia and biconcave flattened vertebrae (10,11).

The gene *COL1A1* (OMIM 120150) is located on chromosome 17q21.33 and is associated with autosomal dominant OI type I (11). Variants in both *COL1A1* and *COL1A2* (OMIM 120160) affect the structural pathways and quantity of type I collagen, thus causing a severe brittle bone skeletal anomaly that may vary from the mild to severe form (8). Type I OI is mostly described by a 50% decrease of collagen type I, typically caused by variants in one of the *COL1A1* alleles (frameshift, nonsense and splice-site changes) that control the mRNA uncertainty and haploinsufficiency (12). The pathogenic variants might also cause complete removal of the *COL1A1* allele (13). Patients with OI type I might have mild to severe features, and the number of fractures varies from patient to patient, even within the same family. Fractures are usually produced when the children begin to ambulate. DI is not usually the main feature of type I OI; however, mild tooth deformities may be observed. To date, 1,169 variants have been reported in the *COL1A1* gene associated with dominant OI (HGMD; http://www.hgmd.cf.ac.uk/ac/index.php).

Type II OI (COL1A1, COL1A2: OMIM 166210). Type II OI is a very severe and perinatal lethal form of OI. Type II OI is caused by pathogenic variants in both *COL1A1* and *COL1A2* genes located on chromosomes 17q21.33 (51 exons) and 7q21.3 (52 exons), respectively (14). The affected individuals have severe skeletal features, such as deformities in the ribs and vertebrae, a short stature and stiffness of the long bones, leading to skeletal fractures. Moreover, other manifestations, such as lung failure, respiratory complications, blue sclera, pulmonary hypoplasia, ultimately leading to mortality, central nervous system malformations and DI are observed (10). The skull is typically very delicate and large, with numerous fractures observed after birth, large fontanelles, wormian bones, platyspondyly, tibial bowing and nonimmune hydrops also observed (8,9). To date, 598 variants have been reported in the *COL1A2* gene associated with dominant OI (HGMD; http://www.hgmd.cf.ac.uk/ac/index.php).

Type III OI (COL1A1, COL1A2: OMIM 259420). OI type III is a rare and severe brittle bone disorder caused by variants in the *COL1A1* and *COL1A2* genes. Affected individuals exhibit features, such as a triangular face, micrognathia, blue sclerae, scoliosis, codfish vertebrae, kyphosis, pulmonary hypertension, DI (both of primary and secondary teeth), bending of the long bones, under-mineralized calvarium, hearing impairment, wormian bones, severe generalized osteoporosis, and respiratory and pulmonary complications (3).

Type IV OI (COL1A1, COL1A2: OMIM 166220). OI type IV (MIM 166220) has a broad range of phenotypic overlapping with OI type I and type III. Type IV OI is also caused by pathogenic variants in the *COL1A1* and *COL1A2* genes, and inherited in an autosomal dominant manner. Clinical manifestations of affected individuals include DI, hearing impairment, otosclerosis, dwarfism, grayish or white sclera mild-moderate skeletal deformity, wormian bones, kyphosis, scoliosis, and long bone fractures (15). Moreover, affected individuals also exhibit other phenotypes, such as multiple fractures, different levels of abnormality, sclera color change, bent bones, cranial settling, joint laxity and scoliosis (8).

Type V OI [interferon induced transmembrane protein 5 (IFITM5): OMIM 610967]. Glorieux *et al* (16) observed OI in individuals with autosomal dominant disorder, having similar phenotypes to OI Sillence type IV. As variants were not identified in the *COL1A1* and *COL1A2* genes, a new type of OI was classified, termed OI type V (OMIM 610967). Variants in *IFITM5* (OMIM 614757) have been found to be associated with dominant OI type V. The *IFITM5* gene is located on chromosome 11p15.5, having 02 exons encoding 132 amino acids and which is critical for early bone mineralization (17). The common characteristics of type V OI include a short stature, triangular faces,

Table I. OI types, genes, genetic position and type of disorder.

Location	Phenotype	Inheritance	Phenotype OMIM no.	Gene/locus	Gene/locus OMIM no.	
17q21.33	Osteogenesis imperfecta, type I	AD	166200	*COL1A1*	120150	Mildest form. Fractures occur after birth. Blue sclerae, hearing loss, normal or near-normal stature.
7q21.3	Osteogenesis imperfecta, type II	AD	166210	*COL1A2*	120160	Most severe form. Lethal in perinatal period. Extreme bone fragility, multiple fractures, underdeveloped lungs.
7q21.3	Osteogenesis imperfecta, type III	AD	259420	*COL1A2*	120160	Severe form. Frequent fractures, bone deformities, short stature, blue sclerae, dental issues. Often wheelchair-bound.
7q21.3	Osteogenesis imperfecta, type IV	AD	166220	*COL1A2*	120160	Moderate severity. Fractures, short stature, normal sclerae, mild to moderate bone deformities.
11p15.5	Osteogenesis imperfecta, type V	AD	610967	*IFITM5*	614757	Hyperplastic callus formation, calcification of interosseous membranes, no dentinogenesis imperfecta, white sclerae.
17p13.3	Osteogenesis imperfecta, type VI	AR	613982	*SERPINF1*	172860	Progressive deforming OI. Hypermineralized bone. Often begins with fractures postnatally.
3p22.3	Osteogenesis imperfecta, type VII	AR	610682	*CRTAP*	605497	Moderate to severe OI. Short humerus and femur, coxa vara, white sclerae, rhizomelia.
1p34.2	Osteogenesis imperfecta, type VIII	AR	610915	*P3H1*	610339	Severe, often lethal. Extreme growth deficiency, under-mineralized bones, rib fractures, pulmonary complications.
15q22.31	Osteogenesis imperfecta, type IX	AR	259440	*PPIB*	123841	Severe to lethal OI. Progressive deforming with prenatal onset.
11q13.5	Osteogenesis imperfecta, type X	AR	613848	*SERPINH1*	600943	Moderate to severe OI. Collagen folding defect leading to brittle bones and frequent fractures.
17q21.2	Osteogenesis imperfecta, type XI	AR	610968	*FKBP10*	607063	Progressive deforming. Severe contractures of large joints, scoliosis, white sclerae, dentinogenesis imperfecta.
12q13.13	Osteogenesis imperfecta, type XII	AR	613849	*SP7*	606633	Moderate to severe OI. Bone deformities, frequent fractures, dental issues, short stature.
8p21.3	Osteogenesis imperfecta, type XIII	AR	614856	*BMP1*	112264	Severe OI. Fractures, deformities, short stature. Associated with abnormalities in bone matrix formation.
9q31.2	Osteogenesis imperfecta, type XIV	AR	615066	*TMEM38B*	611236	Progressive OI. Early onset fractures, bone deformity, short stature, white sclerae.
12q13.12	Osteogenesis imperfecta, type XV	AR	615220	*WNT1*	164820	Severe OI. Early onset, severe deformities, progressive bone fragility, dental problems.

Table I. Continued.

Location	Phenotype	Inheritance	Phenotype OMIM no.	Gene/locus	Gene/locus OMIM no.	
11p11.2	Osteogenesis imperfecta, type XVI	AR	616229	*CREB3L1*	616215	Moderate to severe OI. Progressive deformities and fractures, white sclerae, and dental abnormalities.
5q33.1	Osteogenesis imperfecta, type XVII	AR	616507	*SPARC*	182120	Moderate to severe OI. Progressive skeletal deformities, white sclerae, fractures from birth.
6q14.1	Osteogenesis imperfecta, type XVIII	AR	617952	*TENT5A*	611357	Severe OI. Multiple fractures at birth, short stature, pulmonary complications, progressive deformities.
Xp22.12	Osteogenesis imperfecta, type XIX	XLR	301014	*MBTPS2*	300294	Severe OI with craniofacial anomalies. Blue sclerae, frequent fractures, short stature, dental issues.
15q25.1	Osteogenesis imperfecta, type XX	AR	618644	*MESD*	607783	Moderate to severe OI with delayed motor milestones, short stature, frequent fractures.
7p22.1	Osteogenesis imperfecta, type XXI	AR	619131	*KDELR2*	609024	Moderate OI with dentinogenesis imperfecta, delayed motor milestones, fractures, and short stature.
22q13.2	Osteogenesis imperfecta, type XXII	AR	619795	*CCDC13*	618788	Severe OI. Early onset fractures, white sclerae, significant deformities.
11q23.3	Osteogenesis imperfecta, type XXIII	AR	620639	*PHLDB1*	612834	Severe OI. Frequent fractures, bone deformities, short stature.

moderate to severe bone fragility, varying degrees of multiple fractures, biconcave vertebrae, decreased bone mineral density, wedge-shaped vertebrae, limited pronation/supination of the forearm, hyperplastic callus and hyperextensible joints (18).

5. Classification of autosomal recessive OI and unclassified OI

Type VI OI [serpin family F member 1 (SERPINF1): OMIM 613982]. OI type VI is a rare form, inherited as an autosomal recessive entity (19). It is a rare phenotypic condition caused by the variants in the *SERPINF1* (OMIM 172860) gene. It is located on chromosome 17p13.3 and has a total of 08 exons. Individuals with type VI OI have elevated levels of alkaline phosphatase and a 'fish-scale' appearance of bone (19,20). The distinctive characteristics of type VI OI include a short stature, wormian bones, joint hypermobility, scoliosis, kyphosis osteopenia, upper and lower long bone fractures, blue sclerae and gross motor delay (21). At birth, affected individuals are healthy; however, gradually the phenotypes are revealed, as disease onset is late, and results in severe skeletal abnormalities (10,22). Although osteoid accumulation indicates a mineralization complication similar to osteomalacia, there are no malformations in calcium, phosphate, parathyroid hormone or vitamin D metabolism (1).

Type VII OI [cartilage-associated protein (CRTAP): OMIM 610682]. The first genetic cause of lethal recessive OI was described in 2006, when a mutation in the *CRTAP* gene (OMIM 605497) was identified, leading to OI type VII (OMIM 610682) (23). *CRTAP* is located on chromosome 3p22 and encodes a cartilage-associated protein, which is a key component of a complex involved in the post-translational modification of the α-chain helical region. Of note, 2-3% of cases of OI are lethal due to mutations in the *CRTAP* gene (23,24). The clinical manifestation of type VII exhibits moderate to severe bone abnormality, fragility, the absence of DI and blue sclera. Moreover, it also causes the shortening of the femur and humorous (1,25).

Type VIII OI [prolyl 3-hydroxylase 1 (P3H1): OMIM 610339]. Type VIII OI is a recessive autosomal inherited condition that can be produced by a homozygous pathogenic variation in the *P3H1* gene (OMIM 610339) located on chromosome 1p34.2 and contains 14 exons, and encodes prolyl 3-hydroxylase 1 protein. Children with type VIII OI have progressive

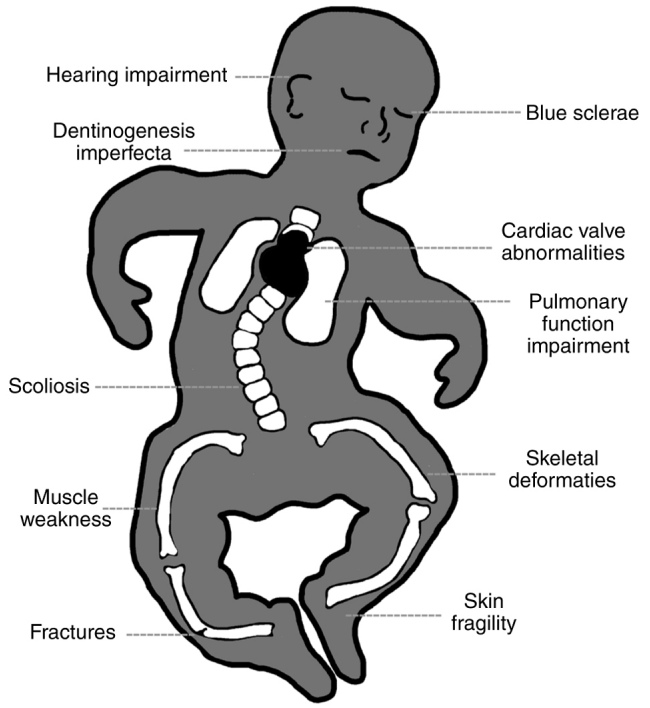

Figure 1. Illustration of the different clinical representations of patients with osteogenesis imperfecta.

abnormalities, white sclera, mineralization of skeleton, severe rhizomelia and dwarfism (26).

Type IX OI [peptidylprolyl Isomerase B (PPIB): OMIM 123841]. Type IX OI is a recessive disorder that can be produced by a homozygous pathogenic variation in the gene *PPIB* (OMIM 123841) located on chromosome 15q22.31, containing 05 exons and causing progressive skeleton abnormalities. The clinical manifestation of type IX OI is similar to that of types II or III, while DI is completely absent (27), translating a cyclophilins (Cyps) family protein known as CyPB (28). Cyps are peptidyl prolylcis trans isomerases (PPIases) that are involved in catalyzing the *cis-trans* isomerization of various peptide bonds. It has dual roles in the prolyl-3 hydroxylation and prolyl *cis-trans* isomerization of type I pro-collagen (29). Changes in the PPIB gene affect collagen production and the adjusting complex contains *P3H1*, *CRTAP* and *CyPB* genes. It also causes a reduction in the amount of *cis-trans* isomerization and a complete change in collagen type I (30). The distinct features of type IX OI are severe abnormalities, blue sclera, short stature, and reduced bone mass density with numerous fractures (31).

Type X OI [serpin family H member 1 (SERPINH1): OMIM 600943]. Type X OI is a recessive autosomal inheritance condition produced by the change in the *SERPINH1* (OMIM 600943) gene located on chromosome 11q13.5 and comprising 05 exons. Common characteristics of type X OI are multiple bone deformities and fractures, DI, generalized osteopenia and blue sclera. The gene *SERPINH1* binds specifically to collagen; it functions as a chaperone in the endoplasmic reticulum and children with this variation have cells that do not synthesize the extra-modified type I collagen (32). Moreover, individuals with type X OI have severe abnormalities and renal stones (10).

Type XI OI [FKBP prolyl isomerase 10 (FKBP10: OMIM 607063]. The autosomal recessive gene *FKBP10* (OMIM 607063) resides on chromosome 17q21.2 and comprises of 10 exons (33,34). It causes severe progressive fractures, distortion, congenital joint contractures and Kuskokwim syndrome. It translates to a protein known as FKBP65 protein with a molecular weight of 65 kDa (35). It has a chaperone function, situated in the endoplasmic reticulum in colocalization with tropoelastin, serving in the bending of the three coils of procollagen. The chaperone function is associated with the disulfide isomerase protein and other functions of peptidyl-prolyl isomerase, which supports the bending of tropoelastin (36). Individuals with type XI OI do not have DI (36,37). Currently, in the *FKBP10* gene, 28 variations have been recorded in different families belonging to different regions of the world (38).

Type XII OI (SP7: OMIM 606633). Type XII OI appears in both an autosomal recessive and dominant manner (39,40), caused by variants in the *SP7* (OMIM 606633) gene located on chromosome 12q13.13, containing 02 exons. Individuals with type XII OI are characterized by recurrent fractures, mild bone abnormalities, osteoporosis, late discharge of teeth, lack of DI, white sclera and abnormal hearing. Furthermore, the bowing of the lower limbs and a short stature have also been reported in patients with type XII (41).

Type XIII OI [bone morphogenetic protein 1 (BMP1): OMIM 112264]. OI type XIII is a recessive autosomal inheritance underlined by variants in the *BMP1 (*OMIM 112264) gene located on 8p21.3 chromosome with 16 exons (42). It encodes the protein bone morphogenetic protein 1 (osterix) responsible for the osteoblast differentiation. Individuals with type XIII OI have severe bone deformities, blue sclera and severe growth deficiency (12). They also have recurrent bone fractures and hyperextensible joints with a high bone mass density (10).

Type XIV OI [transmembrane protein 38B (TMEM38B): OMIM 611236]. OI type XIV is a recessive inherited condition produced by the change in the *TMEM38B* (OMIM 611236) gene located on chromosome 9q31.2 comprising 06 exons. The diagnostic characteristics of patients with type XIV are severe multiple fractures, osteopenia, with normal hearing, dentition and sclera. Fractures mostly occur at the age of 6 years (35). The *TMEM38B* gene encodes TRIC-B, which plays a vital role in intracellular calcium signaling. Complications in TRIC-B produce defective calcium signaling in bone cells causing type XIV OI (12).

Type XV OI (WNT1: OMIM 164820). Type XV is an autosomal recessive inherited disorder that has been nominated based on the detection of a heterozygous variation in the *WNT1* (OMIM 164820) gene. It underlies on chromosome 12p13.12 comprising 4 exons (43,44). Children with type XV OI have recurrent fractures, dwarfism, bone deformities and blue sclera respectively, and cause death of early infants. It is documented that *WNT1* hypofunctional alleles affect clinical with reduce bone mass density in humans, platyspondyly, and bending of upper and lower limb bones (44,45). The *WNT1* gene protein plays a vital role in the β-catenin system, which activates bone synthesis (44,46).

Type XVI OI [CAMP responsive element binding protein 3 like 1 (CREB3L1): OMIM 616215]. Type XVI is a recessive inherited condition caused by variations in the *CREB3L1* (OMIM 616215) gene located on chromosome 11p11.2 comprising 3 exons, causing a severe demineralization, reduced ossification of the skull, blue sclera, multiple fractures in ribs and long bones extremities in the prenatal stage (47). This protein is generally translated by the gene located in the endoplasmic reticulum membrane. However, with pressure to the endoplasmic reticulum, the present protein is modified and transferred to the cytoplasmic transcription factor domain and then translocates to the nucleus. It motivates the transcription of mark genes by attaching to box B elements (48).

Type XVII OI [secreted protein acidic and cysteine rich (SPARC): OMIM 182120)]. Type XVII is an autosomal recessive disorder caused by a mutation in the *SPARC* (OMIM 182120) gene. In humans, the *SPARC* gene underlies on chromosome 5q31.1, comprising 10 exons (49). Osteonectin is a glycoprotein in the bone that attaches to calcium. It is released by osteoblast at the time of bone synthesis, inducting mineralization and promoting mineral crystal synthesis. Osteonectin also indicates the attraction for collagen, adding to bone calcium crystals (50). The individuals with type XVII have features, such as blue sclera, bowing of the spine (scoliosis), hearing impairment, dwarfism, joint complications (contractures), DI and respiratory issues (51).

Type XVIII OI [terminal nucleotidyltransferase 5A (TENT5A): OMIM 611357]. OI type XVIII is a recessive condition, caused by a homozygous change in the *TENT5A* gene (OMIM 611357), located on chromosome 6q14.1 and comprising 03 exons. The *TENT5A* gene encodes the protein terminal transferase 5A protein. Common characteristics of type XVIII OI are the congenital bending of long bones, blue sclera, wormian bones, vertebral failure, and multiple fractures in the first years of life (52).

Type XIX OI [membrane bound transcription factor peptidase, site 2 (MBTPS2): OMIM 300294]. The X link recessive gene *MBTPS2* is located on chromosome Xp22.12, comprising 7 exons. It was identified in type XIX OI. Homozygous or compound heterozygous variants in *MBTPS2* (OMIM 300294) gene are characterized by prenatal fractures and generalized osteopenia, dwarfism, scoliosis, skeleton deformity and marked anterior angulation of the tibia underlies type XIX OI (53).

Type XX OI [mesoderm development LRP chaperone (MESD): OMIM 607783]. OI type XX is an autosomal recessive inherited disorder, caused by a homozygous variant in the *MESD* (OMIM 607783) gene located on chromosome 15p25.1, containing 3 exons. *MESD* gene translates an endoplasmic reticulum chaperone protein for the recognized wingless associated integration site signifying receptors LRP5 and LRP6. Knockout of the *MESD* gene produces embryonic lethality in mice; thus, OI-related alterations act as hypomorphic alleles, since these alterations occur downstream of the chaperone action domain, but upstream of the endoplasmic reticulum maintenance domain. Individuals with type XX OI have blue sclera, dwarfism, joint contractures, hearing loss and scoliosis. Moreover, patients have progressive anomalies of bone complications categorized by osteopenia and a some patients have succumbed due to respiratory failure (54).

Type XXI OI [KDEL endoplasmic reticulum protein retention receptor 2 (KDELR2): OMIM 619131]. OI type XXI is an autosomal recessive inherited disorder. Variants in *KDELR2* (OMIM 609024) underlie type XXI OI. Type XXI OI is characterized by the failure to thrive, a short stature, bowed limbs, wormian bones, joint hypermobility, chest deformity, hypotonia and dysmorphic facies. In addition, the Pakistani girl (55) and the Turkish boy (56) had DI, blue sclerae, scoliosis, femoral fracture and platyspondyly (55,56). The KDELR family of proteins is essential for inter-organelle communication by controlling protein trafficking between the endoplasmic reticulum and Golgi apparatus (57). KDELR2-associated OI results from the failure of heat shock protein 47 (HSP47) to interact with KDELR2, leading to the failure of HSP47 to detach from collagen (55).

Type XXII OI [coiled-coil domain containing 134 (CCDC134): OMIM 618788]. Osteogenesis imperfecta type XXII (OI22) is a severe recessive form of the disease clinically characterized by a short stature, intrauterine growth retardation, multiple fractures at early childhood or birth, bowed and thin long bones, wormian bones, the low mineral density of bones, scoliosis and pseudoarthroses, and slightly gray or white sclerae with absent DI (58,59). Variants in *CCDC134* (OMIM 618788) are responsible for a severe form of OI, XXII OI. *CCDC134* encodes a secreted coiled-coil domain-containing protein, involved in the inhibition of phosphorylation of MAPKs, such as cJun N-terminal kinase (JNK) or ERK (60).

Type XXIII OI [pleckstrin homology like domain family B member 1 (PHLDB1): OMIM 612834)]. Osteogenesis imperfecta type XXIII is a mild form of osteogenesis imperfecta caused by variants in the *PHLDB1* gene (OMIM 612834). Type XXIII OI is clinically characterized by the broadening of the wrists, motor delays, blue sclerae, bowing of the lower extremities, platyspondyly, osteopenia, shallow acetabulum, enlarged proximal femoral metaphysis, metaphyseal cupping, femoral cortical bone erosion with new bone formation and widened metaphysis at the proximal tibia and distal femur (61). PHLDB1 encodes the PHLDB1 protein, which plays a role in insulin-dependent Akt phosphorylation.

Unclassified type OI [plastin 3 (PLS3); OMIM 300131]. An unclassified type of OI is X-linked disorder underlined by variants in *PLS3* (OMIM 300131). Clinical features observed in patients having a variant in *PLS3* include impaired growth, inadequate bone mineralization, reduced bone density, blue sclerae and kyphosis, and fractures in the thoracic and lumbar vertebrae. In addition, slender long bones with thin cortices and wormian bones are observed (62,63).

6. Variant spectrum of OI

Through the analysis of the mutation spectrum of different genes underlying OI, the HGMD was accessed on February 22, 2024. The search revealed a notable concentration of variants (711) reported in the *COL1A1* gene, predominantly associated

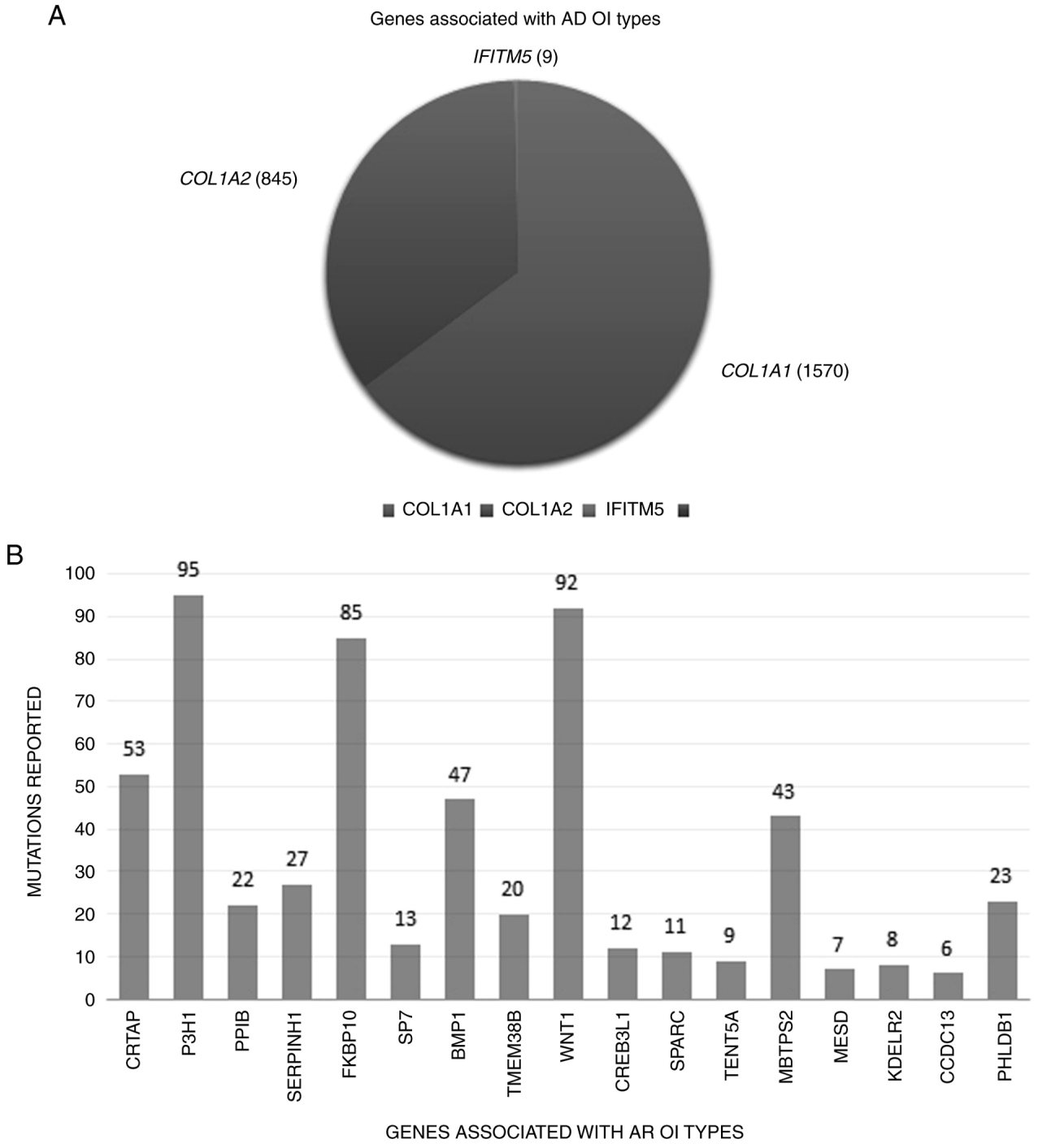

Figure 2. (A) Genes associated with AD OI and the mutations identified to-date. (B) Mutations reported in the genes associated with AR OI. OI, osteogenesis imperfecta; AD, autosomal dominant; AR, autosomal recessive; *IFITM5*, interferon induced transmembrane protein 5; *COL1A1*, collagen type I alpha 1 chain; *COL1A2*, collagen type I alpha 2 chain; *CRTAP*, cartilage-associated protein; *P3H1*, prolyl 3-hydroxylase 1; *PPIB*, peptidylprolyl Isomerase B; *SERPINH1*, serpin family H member 1; *FKBP10*, FKBP prolyl isomerase 10; *BMP1*, bone morphogenetic protein 1; *TMEM38B*, transmembrane protein 38B; *CREB3L1*, CAMP responsive element binding protein 3 like 1; *SPARC*, secreted protein acidic and cysteine rich; *TENT5A*, terminal nucleotidyltransferase 5A; *MBTPS2*, membrane bound transcription factor peptidase, site 2; *MESD*, mesoderm development LRP chaperone; *KDELR2*, KDEL endoplasmic reticulum protein retention receptor 2; *CCDC134*, coiled-coil domain containing 134; *PHLDB1*, pleckstrin homology like domain family B member 1.

with OI type I (OI1; Fig. 2). Clinically, fractures in bones are a common manifestation across various types of OI, apart from OI IV and OI XV. By contrast, DI, characterized by abnormal dentin formation, is least reported and primarily observed in OI types III (OI3), IV (OI4) and X (OI10; Fig. 3). This elucidates the diverse genetic landscape and clinical presentations within the spectrum of osteogenesis imperfecta, highlighting the importance of comprehensive genetic analysis and phenotypic characterization in clinical practice.

7. Challenges in diagnosis

Diagnosing the various genes underlying OI can be challenging due to the variability in clinical manifestations and the high

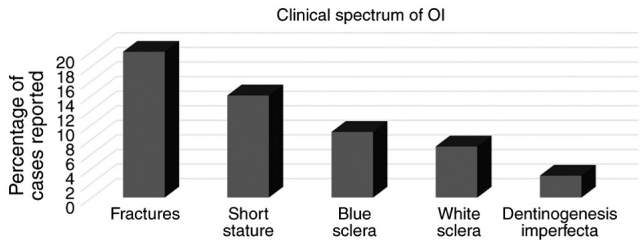

Figure 3. Clinically, fractures in bones are a common manifestation across various types of OI, except for OI4 and OI15. Dentinogenesis imperfecta, characterized by abnormal dentin formation, is least reported and primarily observed in OI types III (OI3), IV (OI4) and X. OI, osteogenesis imperfecta.

degree of overlap in phenotypes. The variable clinical manifestations observed may be attributed to factors, such as epigenetics, modifiers, and environmental influences (64). Next-generation sequencing (NGS) addresses phenotypic variability, facilitating accurate diagnosis. In recent years, prenatal genetic screening and newborn screening have been greatly enhanced by affordable and rapid NGS technologies (65). These technologies analyze cell-free DNA from maternal plasma, providing highly sensitive tests for detecting fetal aneuploidies. Additionally, they enable early detection of monogenic disorders during pregnancy (PGT-M) (66). As NGS technology improves and becomes more affordable, with a reduced data-analysis time, the use of cell-free nucleic acid sequencing is poised to play a growing role in prenatal screening, diagnosis, monitoring, and risk assessment for both fetal and maternal conditions (67).

8. Management and treatment of OI

When the individual is clinically diagnosed with OI, the management of such an individual is determined by the multidisciplinary group, which plays a crucial role in the treatment of OI in children and adults. The majority of affected individuals, not only have recurrent fractures and severe bending abnormalities of the long bones and leg joints, but also connective tissue-related complications (5).

Growth hormone therapy. Growth hormone is related to the anabolic actions of bone. Randomized controlled clinical trials have analyzed the effects of treatment with bisphosphonates (neridronate) and growth hormone in babies with severe to mild OI (68). Researchers have aimed to determine whether the combination of bisphosphonates (neridronate) and growth hormone can accelerate the bone metabolism of children with OI, who are already being treated with bisphosphonates (neridronate). The use of the combined drug was found to improve bone mineral mass at the lumber spine, as well as the preserved area and wrist (69).

Surgical therapy. The common surgical procedure for patients with OI is 'rodding' which involves the placement of metal in the long bones of arms and legs. This surgically fitted rod will lead to the strengthening of bones and will help prevent fractures. The main aim of surgical treatment is to treat anomalies and to decrease bone softness, which prevents complicated bowing and sets the phenotypic condition of the patients. Stapedectomy is used to treat hearing loss caused by otosclerosis otosclerosis (70).

Cyclical bisphosphonate therapy. Cyclic bisphosphonate therapy suppresses pain and enhances the physical mobility of children with OI. Bisphosphonates are known to be potent drugs, which exert prominent antiresorptive effects on bones. This class of agents include etidronic acid, alendronic acid, pamidronic acid, ibandronic acid, clodronic acid, risedronic acid, tiludronic acid and zoledronic acid. They are employed in the management and prevention of glucocorticoid-induced osteoporosis, post-menopausal osteoporosis, osteoporosis due to malignant disease, hypercalcemia of malignancy, and Paget's disease of bone (71).

Physical therapy. The purpose of treatment for patients is to reduce pain and fractures and to enhance flexibility. Physical therapy or treatment is particularly essential in children to increase weight bearing and avoid fractures, as well as to enhance power and flexibility during fracture improvement. A physical treatment is a program that can involve improving deltoids, biceps and essential lower muscles, such as gluteus maximus, gluteus medius and trunk extensors (1).

9. Novel therapeutic approaches for OI

Novel therapeutic approaches focus on targeting the underlying genetic and molecular causes of OI, moving beyond traditional treatments like bisphosphonates. Recent innovations include the following:

Gene therapies. OI is caused primarily by mutations in collagen genes (e.g., *COL1A1* and *COL1A2*), which lead to defective collagen production. Advancements in gene editing techniques, such as CRISPR/Cas9 provide the potential to directly correct these mutations at the genetic level, restoring normal collagen production. Ongoing research aims to fine-tune delivery mechanisms and ensure the safety of these treatments, as demonstrated by Schindeler *et al* (72).

Bone-targeting agents. New drugs are being developed to target bone metabolism more effectively. For instance, sclerostin inhibitors, such as romosozumab can increase bone formation, while reducing bone resorption, offering dual-action benefits. These agents are being investigated for their ability to strengthen bones more robustly compared to bisphosphonates, as demonstrated by Xu *et al* (73).

Precision medicine. Tailored therapies based on the specific genetic mutation of an individual are being explored. For example, different mutations in the *COL1A1* gene may respond differently to treatments, leading to the development of therapies that are personalized based on the type and severity of the mutation. This precision approach is still emerging, but has the potential to revolutionize the treatment of OI by provioding more targeted and effective therapies (74).

Multidisciplinary care, physical and occupational therapy. While the importance of a multidisciplinary care team for patients with OI is widely acknowledged, research indicates that combining various specialties (orthopedics, endocrinology, rehabilitation, genetics and mental health) into a cohesive team can significantly improve quality of life and outcomes.

Similarly, while traditional rehabilitation efforts have focused on physical therapy to enhance mobility and avoid fractures, the role of adaptive devices, orthotic therapies, and continued occupational therapy for improving everyday life skills should be emphasized (75).

10. Conclusions and future perspectives

OI is a heterogeneous group of phenotypic disorders with molecular diversity. In molecular diversity, groups of genes are involved, and mutations in these genes lead to impairments in the production of type I collagen, resulting in abnormal growth synthesis with reduced bone mass density and an increased risk of fractures. Of note, 90% of cases of OI are caused by variants in type I collagen. There are almost no data available concerning the treatment of OI related to patients in Pakistan and Saudi Arabia. This gap underlines the importance of further region-specific studies to determine the effectiveness and safety of the current therapeutic options, including the use of bisphosphonates, surgery and physical therapy, among others. The present short and coherent review summarizes a total of 20 genes that cause OI type I to type XX; among these, five genes are autosomal dominant, and the remaining 15 genes are autosomal recessive. In the recessive condition, the gene *MBTPS2* is located on the X chromosome. It is a curable pediatric syndrome, and there are no local published data concerning therapy in children with OI in Pakistan and Saudi Arabia. The present review provides some knowledge for the concerned pediatricians, researchers and family physicians for the preliminary assessment and management of OI in children. Currently, there are therapeutic approaches available, such as bisphosphonates, growth hormone and gene therapies. Cyclical bisphosphonate treatment has a positive effect on the rate of fractures, bone mineral mass, mobility score and pain episodes. Currently, surgical therapy is also valuable to a certain extent. Moreover, the present review also summarized management policies, in an aim to provide insight into the treatment of this disease and to enhance the understanding of OI.

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HK and ZA wrote the review. HK performed the literature search and collected data from the relevant literature, while ZA contributed to the analysis and interpretation of the data. MU reviewed the manuscript and supervised the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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