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Molecular Diversity of Osteogenesis Imperfecta

Feroz Khan [1], Shah Hussain [2], Muhammed Asim Khan [3], Niamat Ullah [4], Syed Shahab Ud Din Shah [2*]

[1] Department of Zoology and Biology, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan
[2] Department of Biochemistry, Quaid-i-Azam University, Islamabad, Pakistan
[3] Department of Zoology, Quaid-i-Azam University, Islamabad, Pakistan
[4] Department of Pharmacy, University of Malakand, Pakistan

ABSTRACT

Osteogenesis imperfecta is a hereditary abnormality marked by extreme bone fragility, osteoporosis, and diminished bone mineral density. It is due to the mutation in genes like COL1A1 and COL1A2 responsible for the synthesis of type I collagen. 90% of osteogenesis imperfecta is stated to be produced by dominant autosomal mutations such as COL1A1 or COL1A2 mutations, while 10% of osteogenesis imperfecta is caused by recessive autosomal mutations such as SERPINF1, LEPRE1, SP7, SERPINH1, FKBP10, PLOD2, PPIB, and CRTAP alterations. 20 genes that are linked with osteogenesis imperfecta type I to type XX are discussed in this review article. Among these genes, 5 genes are associated with autosomal dominant, 14 genes causing autosomal recessive and MBTPS2 is located on the X chromosome which is associated with X-linked recessive. Cyclical bisphosphonate therapy has been found to have a positive effect on fracture incidence, bone mineral mass, agility score, and episodes of pain. Similarly, growth hormone therapy and surgical therapy are also valuable to some extent. This study would provide knowledge for clinicians and researchers in search of a better understanding of osteogenesis imperfecta and to combat this disease.

Key words: Osteogenesis, Imperfecta, COLIA1, COLIA2, OI

1. INTRODUCTION

Osteogenesis imperfecta (OI) or "brittle bone disease" is a heritable genetic abnormality characterized by severe bone fragility, osteoporosis, and reduced bone mineral density [1-2]. It is mostly caused by alteration in genes such as COL1A1 and COL1A2 responsible for collagen type 1 production. Mutations in these genes result in the production of defective collagen that affects bones rather than other organs of the body [3]. It is documented that 90% of OI disease is produced by dominant autosomal genes like COL1A1 or COL1A2, while 10% of the disease is caused by 08 autosomal recessive genes like SERPINF1, LEPRE1, SP7, SERPINH1, FKBP10, PLOD2, PPIB, and CRTAP

[4]. These OI types have variable symptoms that start from mild to severe. OI patients are characterized by having features such as fragile bones, short stature, raspatory tract problems, hair loss, dentinogenesis imperfecta (DI), skeletal anomalies, triangular face, blue sclera, bowed of arms and legs, scoliosis, ligaments problems, and tendon rupture [5]. Musculoskeletal anomalies along with bone anomalies including anterior bending of femur, tibia, and fibula and lateral bending of radius, ulna, and femur of legs. In severe OI case bone fractures are observed at the beginning of life and long bones are frequently involved. Femoral fractures are the most frequent fractures of the long bones, where the fractures occurred at convexity of bone. The degree of severity of manifestation like scoliosis, DI, and bone softness can be very diverse from one subject to another, even if both subjects exist in the same OI type [6].

1.1. Collagen

The unique type of collagen molecule formed as procollagen is assembled during bone formation, and N-terminus and C-terminus pro-peptides are then cut. In the bone matrix, the largest component of the molecule, the triple helix of collagen, is assimilated. This specific type of collagen is called type 1 collagen. Collagens include a large group of triple-helical proteins and are the most plentiful protein in vertebrates, indicating 30% of the total proteins. There are 29 genetically different types of collagens that are translated by 44 different genes [7]. Based on molecular structure and assembly style, they can be categorized into different subgroups [8]. The largest subgroup of the collagen are types I, II, III, V, XI, XXIV and XXVII.

Type I collagen

Collagens especially type I collagen perform an important role in the cell receptors like integrins, discoid in domain receptors and glycoprotein VI etc, which facilitate cell activities and extracellular matrix remodeling [9]. Previous findings have revealed that glycosylation of hydroxylysine remains of collagen perform vital action in the collaboration of several receptors [10,11]. One of the serious reasons for the physical and biomechanical functions of type I collagen fibrils are the post-translational modifications (PTMs) of peptidyl lysine remains. Lysine adjustments of collagen are extremely controlled sequential procedures that take part inner and outside the cell. Inside the cell, precise peptidyl lysine remains both in the helical and non-helical (telopeptide) areas of the molecule can be hydroxylated establishing 5-hydroxylysine. Precise hydroxylysine remains in the helical area can be glycosylated with the accumulation of galactose, a few of which can be more glycosylated with the accumulation of glucose. Precise enzymes catalyze each of these resulting in a domain-specific lysine adjustment in the cell. Outside of the cell, oxidative deamination arises to the telopeptide lysine and hydroxylysine to make the reactive aldehydic remains in the presence of enzyme [11,12]. The developed aldehydes then initiate a series of non-enzymatic compression reactions to produce vast covalent intra- and inter-molecular cross-contacts that are essential for the collagen fibrils' biomechanical tasks [13]. Thus, type I collagen is an extremely examined collagen for its lysine adjustment [12].

Collagen type I biosynthesis

Type I collagen is an elongated chain of molecules ranging from 300 nm long and 1.5 nm thick. Its biosynthesis is a complex procedure including several PTMs, chain-linked and bending secretion, procollagen managing, self-assembly, and developing cross-linking. Nearly 90% of OI patients have

mutations in COL1A1 and COL1A2 genes [14,15]. Type I collagen biosynthesis is completed in two parts (i) outside and (ii) inside of the cell.

1.2. Inside the cell

The synthesis of type I collagen inside the cell can be completed by the following steps:

In nucleus and cytosol of the fibroblast (Osteoblast):

The osteoblast is the part of the fibroblast, where collagen type I is synthesized. Inside the nucleus, there is nuclear machinery that underlies the process of transcription (RNA synthesis). This molecule (mRNA) leaves the nucleus through the nuclear pore and enter the cytosol of the fibroblast, associated with free ribosomes, and start the process of translation. It is made up of two alpha 1 chains and one alpha 2 chain. As a minor form, an alpha 1 homotrimeric form exists. There are three regions of the molecule containing the N-terminal non-triple helical region, the middle triple helical region and the C-terminal non-triple helical region (C-terminal non-triple helical region). More than 95 percent of the molecule suggests the only continuous triple-helical region.

In Rough Endoplasmic Reticulum (rER):

Three pro-alpha chains (two pro-alpha1 and one pro-alpha2) bind together at the side of the C-terminal of the chains that is used in the development of type I collagen in the rER and the triple helix is divided near the N-terminal in a zipper-like fashion to create a procollagen molecule. Numerous enzymes machinery and chaperones are participating in chain connection, maintenance, and appropriate bending [8,16]. Before the synthesis of a triple helix procollagen molecule and the emerging proα chains require numerous PTMs. They consist of proline residue hydroxylation, catalyzed by enzymes such as prolyl-4-hydroxylases and prolyl-3-hydroxylase. With the lowest set of sequence X Pro-Gly, the former answer to proline and the final tends to have a Hyp is hydroxyproline series of arrangements. Proline hydroxylation is essential for the conservation of the conformation of the triple helix. The hydroxylation of both residues like lysine and glycosylation of hydroxylysine also happens enzymatically before the synthesis of a triple-helical procollagen molecule [8].

In Golgi apparatus:

The procollagen proteins are then shipped from the rER to the parts of the Golgi apparatus and are produced to the extracellular space. This procollagen has uncoiled free end of both sides called as propeptide site containing disulfide bond are together and transported to the Golgi apparatus in the form of vesicles. These vesicles are then released from the cell by the process of exocytosis.

1.3. Outside the cell

The free procollagen molecules are combined with an enzyme called peptidase that cleaves at the propeptide site, which gives rise to collagen monomer. These monomers are unstable and form a strong covalent bond for the stabilization in the presence of an enzyme called lysooxidase and thus synthesize type I collagen [8].

Collagen type I comprised of two alpha 1 chains and one alpha 2 chain. After the translational process, the pro-a 1 chains and pro-2 chains are synthesized in the rER of the osteoblast cell. These chains are links together at the side of the C-terminal and the triple helix is divided near the N-terminal in a zipper-like manner to produce a procollagen molecule, transported from the rER to the stacks of Golgi apparatus and produced to the outside of the cell.

This procollagen has uncoiled free end of both sides called as propeptides site containing disulfide bond, transported to the Golgi apparatus in the form of vesicles released by exocytosis. These molecules act on peptidase enzyme and cleaved, finally collagen monomer is formed. These monomers are stabilized by the formation of a strong covalent bond, finally strong and stable type I collagen produced which are the important constituents of bone.

2. PREVALENCE OF OI

OI is a rare hereditary brittle bone condition reported in various ethical classes with a different prevalent proportion. The estimated occurrence of about 1/10,000 and 1/25,000 globally. This prevalence is due to the lack of best understanding of problems in the analysis, best cure, and current development about the disease in the world [17]. Similarly, the estimated prevalence was recorded with a range of about 1/10,000 or 1/20,000 live births in America [18]. The prevalence of OI is approximately 6/100,000 or 7/100,000 birth, while in the Netherlands, the incidence of about 5/100,000 live birth [19]. The prevalence of the disease was recorded with more than 1/10,000 individuals in Montreal Canada [20]. In the United States, the prevalence of 8/100,000 individuals, perhaps 30,000 alive with this disease [21]. But the overall prevalence of various types of the disease was recorded at approximately 1/15 000 or 1/20 000 births [22,23]. In other findings, it is indicated that the overall prevalence of the different types of the diseases is approximately 1/15,000 or 1/20,000 births and most of the cases are genetically due to a mutation in COL1A1 or COL1A2 dominant genes [21]. In Pakistan, a total of 72 patients have been reported, among these 40 (55.6%) boys and 32 (44.4%) are girls. Moreover, the mean age was 3.64 ± 3.2 years, while the age range at the beginning of the treatment was 1-13 years [24]. In India, the estimated prevalence is round about 1/20,000 live birth [25]. The clinical features of type I and type II OI were reported 71% and 12% respectively in central Denmark [26]. A British research group found that 79 OI patient deaths occurred between 1980 and 1995 in a cohort of 1,297 survey-recognized and clinically recognized OI patients. The researchers established respiratory tract infection as the most frequent cause of death in OI patients in this study and reported a mean age at death of 6.2 years in the extreme clinical features and 63.5 years in the phenotypes of the milder features [27]. Instead of collagen type 1, it is likely that OI develops diseases in other body part structures. This type 1 collagen is the human body's most common collagen [28,29].

3. MOLECULAR DIVERSITY OF OI

Clinically and genetically OI is classified into various types known as “Genetic Heterogeneity” in OI. It is frequently discussed in an autosomal recessive, autosomal dominant, and X-linked pattern [30].

3.1. Classification of autosomal dominant OI

a. Type I OI (COL1A1: OMIM 166200)

The COL1A1 gene is located on the 17q21.33 chromosome, comprising of 51 exons associated with autosomal dominant OI type I [31]. OI type I patients have no bone abnormality and a considerably different number of fractures, reported from the same family. Bones fractures when the patients start to ambulate [21,30]. The skeletal features of the patients include vertebral fractures which can cause scoliosis. Other features include blue sclera, hearing impairment loss, and aortic regurgitation [32]. The mutational analysis for bone anomalies in mature zebrafish recognized a variant in COL1A1 that exactly models of the human OI [33].

b. Type II OI (COL1A1, COL1A2: OMIM 166210)

The COL1A2 gene is located on the 7q21.3 chromosome, comprising of 52 exons associated with autosomal dominant OI type II. Pathogenic variant in both genes COL1A1, COL1A2 caused an autosomal dominant OI type II [34]. In the utero stage of the individuals have deformities of ribs, vertebrae, short stature, stiffness of long bones lead to a skeletal crake. Moreover, any other manifestations like lung failure, respiratory complications, blue sclera, pulmonary hypoplasia, and ultimately death [27]. Two breeds of dogs, such as Golden Retrievers and Beagles, have been identified in the COL1A1 and COL1A2 variants responsible for the OI condition. Genetic issues with OI have not been clarified in other members of the Canidae family [35,36].

c. Types III OI (COL1A1, COL1A2: OMIM 259420)

OI type III is a rare and severe brittle bone disorder caused by mutations in COL1A1 and COL1A2 genes. Affected individuals having OI type III include features such as triangular face, micrognathia, blue sclerae, scoliosis, codfish vertebrae, kyphosis, pulmonary hypertension, DI (both primary and secondary teeth), bending of long bones, under mineralized calvarium, hearing impairment, Wormian bones, severe generalized osteoporosis respiratory and pulmonary complications [3,37].

d. Type IV OI (COL1A1, COL1A2: OMIM 166220)

Form IV of OI has a wide array of phenotypes overlapping with type I and type III of OI. Type IV OI is also caused in the COL1A1/2 genes by pathogenic mutations and acquired in an autosomal dominant manner. Clinical manifestation of the affected individuals includes hearing impairment, DI, Otosclerosis, dwarfism, grayish or white sclera mild-moderate skeletal deformity, Wormian bones, kyphosis, scoliosis, and long bones fractures [38]. Moreover, the individuals have other phenotypes like multiple fractures, different levels of abnormality, sclera color change, bend bones, cranial settling, joint laxity, and scoliosis [21,30]. The genes of the bone matrix containing COL1A12 and osn display strangely alike expression models. Both genes are expressed in the epidermis region of the zebra fish indicating the fin fold and connective tissue, but osn is expressed in the ear development. This general expression comparatively shows their clarification difficult, mainly with deep bones like parasphenoid [39]. The scientific assessment of skeletal features of zebra fish models underlying different variants in type I collagen of zebra fish containing COL1A (col1a1a, col1a1b) and COL1A2 genes translating α1 and α3 chain respectively. It is also involved in two knockout variants (bmp1a, plod2) indicating severe OI in recessive pattern with faults in type I collagen assessing and cross-linking [40]. During mutational analysis detected a different abnormality of skeletal phenotypes containing callus development, bending, and kinking of the ribs, deformity of the vertebral column, dwarfism, and craniofacial anomalies [41]. In addition, the high protection of osteogenesis production programs between teleost fish and humans, the evaluation of the effective gene and the mechanism of zebrafish may be associated with human skeleton disease [42]. In the recent past, various zebrafish variants have previously been reported to exactly model-specific genetic kinds of human OI [43,44]. However, on a full evaluation of single mutants, these findings were illustrated, revealing several subtypes of OI, while the highest asset of zebrafish resides in the wealth of embracing the parallel assessment of multiple mutant models. Advances in management and evaluation have now

allowed hundreds of phenotypical and densitometric characteristics in broad sets of skeletal varieties of zebrafish to be studied [41,45].

e. Type V OI (IFITM5: OMIM 614757)

The IFITM5 gene is located on the 11p15.5 chromosome, comprising of 2 exons associated with autosomal dominant OI type V [46]. The common characteristics of type V OI are calcification of the forearm interosseous membrane which starts to radial head mobility and callus development (hyperplastic) and long bone fracture can lead to a very hypertrophic callus [47]. Type V OI is temperately bending and patients show mild to severe bone softness [48,49]. In mice, from birth and in the adult stage, the IFITM5 showed bent bones. Shorter appendicular materials but not superficial bone mass factors [50]. Mostly, the human variants comprise a single heterozygous variant (c.-14C>T) causing autosomal dominant OI type V [51]. Late mineralization, utero fractures, and severe skeletal deformity were indicated in mice mutant IFITM5, but perinatal bone mass could not be recognized because of perinatal lethality [52]. Moreover, the hind limb of the mice lacked growth deformities indicating the forelimbs and hind limb fractures as well abnormalities in the rib cage were observed [53]. In transgenic mice, the overexpression of the wild-type form of IFITM5 results in normal growth and development, showing that the potential human variant (c.-14C>T) has a neomorphic influence on the development of bones [52].

3.2. Classification of autosomal recessive OI

a. Type VI OI (SERPINF1: OMIM 172860)

The SERPINF1 gene is located on the 17p13.3 chromosome, comprising of 8 exons associated with autosomal recessive OI type VI [54]. Children with type VI showed alkaline phosphatase and bone-like fish scale, examined under the microscope, and low mineralization [55,56]. At birth, the children are healthy however gradually the disease becomes severe and abnormalities increase with age [32,57]. Although the osteoid accumulation indicates a mineralization complication like osteomalacia, there is no malformation in calcium, phosphate, parathyroid hormone, or vitamin D metabolism [58]. PEDF mice were developed to learn about the function of PEDF in bones and other tissues after it was found that a shift in the SERPINF1 gene in humans produces type VI OI [59]. PEDF is generated mostly at low levels in the liver and bone, and the bone characteristics of type VI OI can be enhanced by PEDF levels. In addition, the helper-dependent adenovirus (HDAd) was used to drive the expression of man SERPINF1 in mouse liver, the bone function was not improved by overexpression of the PEDF [60]. It is documented that the intraperitoneal inoculation of the PEDF comprising microspheres obviously improved bone mass and moderately biomechanical parameters [61].

b. Type VII OI (CRTAP: OMIM 605497)

The CRTAP gene is located on the 3p22.3 chromosome, comprising of 7 exons associated with autosomal recessive OI type VII [62,63]. The biallelic pathogenic change in the CRTAP gene producing complete deterioration of protein function cause OI type VII [62,64]. It is estimated that 2% to 3% cases are caused by the mutation in CRTAP gene [65]. The clinical manifestation of type VII individuals has coxa vera, shortening of the femur and humorous, ligamentous laxity and hearing impairment, blue sclera [58,66]. It is documented that the inherited cause for type VII OI in humans was highly concerned with a scarcity of CRTAP expression, using a homologous recombination process, a strain of homozygous CRTAP deficient mice was created

[64,67]. The CRTAP mice are correctly modelled on OI in humans since they have an exceptionally high mineral volume and elevated mineral densities in their bones compared with wild-type mice [67]. Progressive extreme kyphoscoliosis, reduced bone density, and cartilage anomaly include other characteristics observed in CRTAP mice [68]. However, CRTAP rats tend to have a less extreme variant of the disease than is present in most humans [63,68]. Total skin tensile testing of CRTAP mice found that tissue rigidity was 60 percent smaller than that of mouse skin of the wild type [69].

c. Type VIII OI (P3H1: OMIM 610339)

The P3H1 gene is located on the 1p34.2 chromosome, comprising of 14 exons associated with autosomal recessive OI type VIII and encodes Prolyl 3-hydroxylase 1 protein. Children with type VIII OI have progressive abnormalities, white sclera, mineralization of skeleton, severe rhizomelia, and dwarfism [70]. A homologous genetic recombination technique was employed in 2010 to produce a P3H1 knockout mouse by targeting exons 1 and 3. No OI traits were expressed by the heterozygous P3H1 mice, but homozygous P3H1 mice suggestively exhibited smaller body size, lower mineral density in the skull and long bones, progressive kyphoscoliosis, and short femora with decreased stiffness and failure load consistent with wild type littermates [71]. High auditory thresholds and altered phenotypes of middle-ear bone joints have also been formed by P3H1 mice, rendering them an ideal model for testing the pathways that cause hearing loss in patients with OI [72]. Furthermore, one P3H1 catalytic region amino acid modification containing knockin mice disrupted enzymatic activity while maintaining the ability to bind to CRTAP and form the P3H1 complex, resulting in osteopenia without any apparent impact on the development of the mouse [73]. These factors support the hypothesis that the enzymatic behavior of P3H1 and 3Hyp may be an important condition in mineralized tissues for fibrillary collagen, leading to recessive OI in CRTAP or P3H1 defects [74].

d. Type IX OI (PPIB: OMIM 123841)

Type IX OI is a recessive autosomal inheritance that is located on chromosome 15q22.31 containing 5 exons only. The clinical manifestation of type IX is the resemblance to the types II or III OI without DI [75]. The distinct features of type IX are severe abnormalities, blue sclera, short stature, reduce bone mass density with many fractures are seen [64]. Between 2006 and 2007, separate experiments were carried out on OI, showing the action of P3H1 and CRTAP in the establishment of OI in humans and mice [62,64,70,74]. There has also been a close correlation between P3H1, CRTAP, and PPIB, and it has been seen that they are interrelated in the rough endoplasmic reticulum to create a complex that is known to be a collagen chaperone [62,71,74,76]. To further explore this relation, the Cre/Lox approach was used to render a PPIB knockout mouse by targeting exon 3 by homologous recombination. The heterozygous PPIB mice developed using this technique showed no symptoms of OI and were bred to produce PPIB relatives, which instead show signs of OI, including reduced body size and weight, reduced bone mineral density and volume, progressive kyphosis, reduced skin stiffness and increased laxity [74]. An appropriate type IX OI model is proposed, although the clinical characteristics reported in PPIB mice are low in severity compared to humans [64]. In addition, kyphosis and reduced bone density were caused by homozygous removal of peptidyl-prolyl isomerase caused by PPIB in small mice. It is also recognized that PPIB removal decreased the amount of P3H1 but not CRTAP, suggesting that PPIB is essential for P3H1 stability [74].

e. Type X OI (SERPINH1: OMIM 600943)

The SERPINH1 gene is located on the 11q13.5 chromosome, comprising of 5 exons associated with autosomal recessive OI type X. Common characteristics of type X OI are multiple bone deformities and fractures, DI, osteopenia, and bluish sclera [77]. Moreover, the individuals with type X have severe abnormalities and renal stones [32]. In addition to COL1A1, COL1A2, CRTAP, and LEPRE1, mutations in SERPINH1 are considered to give a respected human medicine model and a fifth OI gene in dogs with OI [78]. Drogemuller and his colleague identified missense mutation in the SERPINH1 gene in Dachshunds (c.977C.T, p.L326P) (Wiene dog) [79]. It has also been reported that fibroblasts of SERPINH1 develop abnormally thin and branched type I collagen fibers [80]. In both tested microsatellites, all dogs carrying OI disease showed homozygosity and both genotyped parents had single copy of the haplotype condition. The investigator showed variants that may be responsible for the OI traits in the canine SERPINH1 gene [79]. In addition, the non-conservative replacement of amino acids may affect SERPINH1's ability to repair and stabilize triple helices of collagen. The mutant p.L326P does not show an entire null allele in OI affected dogs, but has some residual movement, as was seen in SERPINH1 knock-out mice in live-born dogs with extreme OI rather than embryonic lethality. The clinical characteristics of infected dogs primarily display a lack of type I collagen, which is the most prevalent collagen, whilst the basal membranes containing collagen IV do not show some significant adjustments [81].

f. Type XI OI (FKBP10: OMIM 607063)

The FKBP10 gene is located on the 17q21.2 chromosome, comprising of 10 exons associated with autosomal recessive OI type XI [82,83]. It causes severe progressive fractures, distortion, congenital joint contractures, and Kuskokwim syndrome. It translates a protein called as FKBP65 protein with a molecular weight of 65 kDa [84]. It has a chaperone feature, located at colocation with tropoelastin in the endoplasmic reticulum, serving in the bending of the three coils of procollagen [83]. At present, 28 variations have been recorded in the FKBP10 gene in various families belonging to different regions of the world [85]. To understand the role of FKBP10 in mice, the European conditional mutagenesis allele was developed. The clinical characteristics of OI were not reported in the initial development of heterozygotes in the mice. However, late growth and descending facing forelimbs, brittle tissue, flattened facial structures, endoplasmic reticulum (ER) enlargement provided by the set of irregular procollagen chains in the ER and perinatal decease were shown by homozygote mice obtained from breeding. On the other hand, in type XI OI, there was no perinatal decease, the effect of modification on ER, and collagen production is phenotypically like that of FKBP10 in mice. In contrast to the human variant in FKBP10, mice showed perinatal mortality due to embryonic lethality, probably due to vasculature abnormalities, prevalent tissue brittleness or poor lung function. In this way, a conditional knockout mouse model for FKBP10 might be useful for controlling the bone and tendon functions of FKBP10 deletion in postnatal mice [86].

g. Type XII OI (SP7: OMIM 606633)

The SP7 gene is located on the 12q13.13 chromosome, comprising of 2 exons associated with autosomal recessive OI type XII. The individuals with type XII have characterized by recurrent fractures, mild bone abnormalities, osteoporosis, late discharge of teeth, lack of DI, white sclera, and normal hearing. Furthermore, bowing of lower limbs and short stature are also reported [87]. SP7 is a Zn-

finger possessing transcription factor, important for osteoblast differentiation. Sp7 knockout mice are entirely absent from bone growth due to osteoblast difference defects, whereas postnatal exclusion decrease bone mass significantly caused by osteoblast number and function harm [88,89]. Automatically, Sp7 is used for vibrant enhancers of osteoblast target genes through the regulation of compounds that contain distal-less homeobox genes [90]. Interestingly, recessive OI in humans with mild bone malformations and frequent fractures was developed by a frameshift variant [87]. A main technique using homologous embryonic stem cell recombination to produce a Sp7 knockout mouse to generate non-phenotypic heterozygous in Sp7 mice. However, Sp7 null progeny collected from Sp7 couplings all died after few minutes of birth, causing respiratory complications and displaying severe limb abnormalities [88]. The secondary strategy used the Cre/Lox system to make Col1a1 conditional SP7 knockout mice, which without perinatal lethality were scheduled to deactivate SP7. The Col1a1 mice displayed decreased trabecular bone mineralization, osteopenia, and cortical bone cracking. Since both methods existed before SP7 was linked to OI in humans [89].

h. Type XIII OI (BMP1: OMIM 112264)

The BMP1 gene is located on the 18p21.3 chromosome, comprising of 16 exons, associated with autosomal recessive OI type XIII [91]. It encodes the protein bone morphogenetic protein 1 (osterix) responsible for osteoblast differentiation. The children with type XIII have severe bone deformities, blue sclera, and severe growth deficiency are reported [92]. They have also recurrent bone crakes and hyperextensible joints with high bone mass density [32]. The BMP1 variant in zebrafish called frilly fins produces a ruffled larval fin, reduced body axis, deformed craniofacial bones, vertebrae, and brief ossification and bone density (Frf). Missense changes in BMP1 were created by Frf and osteoblasts with an additional cuboidal structure were controlled compared to wild fish [43]. BMP1 was designed to cut and deactivate the chordin of the BMP1 inhibitor, which helps to generate type I developed collagen and hence can disrupt osteogenesis when high levels occur [93]. In addition, BMP1 converts a secreted procollagen C-proteinase that is closely related to the family of tolloid proteases and is functionally distinct from other BMPs producing bones [94]. BMP1 was also revealed to demonstrate protease activity on proteins of the extracellular matrix (ECM) [95,96]. BMP1 mice embryos discovered short ossification of the skull, parietal and interparietal skull bones but no distinct defects of the axial or appendicular skeleton [94]. The lack of strong skeletal properties in BMP1 mice is presumably attributed to tolloid's residual C-proteinase activity as immediate elimination of BMP1 and a suggestive decrease in bone density, weight, and biomechanical properties in perinatal mice due to increased bone turnover [95].

i. Type XIV OI (TMEM38B: OMIM 611236)

The TMEM38B gene is located on the 9q31.2 chromosome, comprising of 6 exons associated with autosomal recessive OI type XIV. The diagnostic characteristic of type XIV patients has severe multiple fractures, osteopenia, with normal hearing, dentition, and sclera. Fractures mostly occurred at the age of 6 years old [84]. The gene TMEM38B translates the TRIC-B, which plays a vital role in intracellular calcium signaling. The complication in TRIC-B produce the defective calcium signaling in bone cells causes type XIV disorder [92]. In mice, the TMEM38B variation resulted in mice die quickly because of after birth due to lung deformities after birth. During birth, these mice show important damage to bone mineralization. Primary calvarial

osteoblasts from mice displayed decreased mineralization despite a rise in collagen protein gathering in the endoplasmic reticulum, representing faults in collagen secretion [97]. Damage of function variations in TMEM38B creates sensible to severe recessive OI [98,99]. Like shown in mice, human fibroblasts from OI patients with TMEM38B variations indicated reduced synthesis, discharge, and accumulation of type I collagen [100].

j. Type XV OI (WNT1: OMIM 164820)

The WNT1 gene is located on the 12p13.12 chromosome, comprising of 4 exons associated with autosomal recessive OI type XV [101,102]. The children with type XV OI have recurrent fractures, dwarfism, bone deformities, blue sclera, and cause the death of early infants. It is documented that WNT1 hypofunctional alleles effect in clinical with reduce bone mass density in humans, platyspondyly and bending of upper and lower limb bones [102,103]. The WNT1 gene protein plays a vital role in the beta-catenin system, which activates the bone synthesis [102,104]. Wnt1 is often referred to in mice as the Swaying (Sw) mouse, with a spinning motion configuration and cerebellar shortage, was first identified as having less defined coordination. The Sw mouse was later generated to be characters like mice developing osteopenia and weak bones with a targeted WNT1 alteration. It was later recognized to be formed by a WNT1 (Wnt1Sw) frameshift upgrade, with homozygous (Wnt1Sw/Sw) mice. Suggesting the features of Sw, such as normal breaks, decreased bone density, and decreased bone strength, repeating human patient characteristics [105–107].

k. Type XVI OI (CREB3L1: OMIM 616215)

The CREB3L1 gene is located on the 11p11.2 chromosome, comprising, of 3 exons associated with autosomal recessive OI type XVI, causing a severe demineralization, reduced ossification of the skull, blue sclera, multiple fractures in ribs, and long bones extremities in the prenatal stage [108]. This protein is generally translated by the gene, located in the endoplasmic reticulum (ER) membrane. The strain to the ER of the present protein, however, is cut and moved to the domain of the cytoplasmic transcription factor translocating to the nucleus. It motivates the transcription of genes from the label by adding elements to box B [109]. CREB3L1 is a simple leucine zipper (bZIP) transcription mechanism that belongs to the CREB/ATF family. It is also called the directly caused material of an aged astrocyte (OASIS), which shares great physical similarity with ATF6. CREB3L1is highly expressed in osteoblasts and, due to reduced osteoblast activity, homozygous elimination in mice causes extreme osteopenia [110]. The genetic function of CREB3L1 found in two parts, such as CREB3L, specifically fixes a UPRE-like order in the Col1a1 promoter region in order to drive its appearance, and also seeks to control the discharge of matrix proteins [111]. In order to create recessively inherited extreme OI with occasional cracks in humans, disruption to function variations in CREB3L1 have been seen [108].

l. Type XVII OI (SPARC: OMIM 182120)

The SPARC gene is located on the 5q31.1 chromosome, comprising of 10 exons associated with autosomal recessive OI type XVII [112]. The individuals with type XVII have features like blue sclera, bowing of spine (scoliosis), hear impairment, dwarfism, joints complications (contractures), DI, and respiratory problems [113]. The northern blot technique indicated that the mutable SPARC expression in all mature mouse tissues with all developing phases was observed. During development, the SPARC expression was higher in extraembryonic tissues than in embryos. Therefore, human and mouse SPARC common the 93% amino

acid identity. This technique indicated differential expression of the main 2.2-kb transcript in all fetal, newborn, mature human tissues and cell positions are observed [114,115]. Moreover, the SPARC lacking mice are produced by targeted disturbance. The mice seemed normal and fertile till about 6 months of age, when they grow causes severe eye pathology considered by cataract creation and break of the lens capsule. The first symbol of lens pathology happened in the equatorial bend area where vacuoles slowly designed within distinguishing epithelial cells and fiber cells. The lens capsule exhibited no qualitative variations in the main basal lamina proteins laminin, collagen IV, and entactin [116].

m. Type XVIII OI (TENT5A: OMIM 611357)

The TENT5A gene is located on the 6q14.1 chromosome, comprising of 3 exons, associated with autosomal recessive OI type XVIII. The TENT5A gene encodes the protein terminal transferase 5A protein. The common characteristics of type XVIII OI are congenital bending of long bones, blue sclera, Wormian bones, vertebral failure, multiple fractures in the first years of life. OI type XVIII was reported in Italian boy causes one base pair duplication in the TENT5A gene, producing frameshift predicted to result in an early termination codon. Similarly, in 4 children belonging to 3 different consanguineous families with type XVIII OI reported mutation performed by the exome sequencing [117]. By analyzing N- ethyl-N-nitrosourea consequent mouse variants for high plasma alkaline phosphatase action, tracked by exome sequencing, recognized heterozygous damage of function change in TENT5A. The change produced early truncation of TENT5A after residue 156. Mice homozygous for the change exhibited a more raise in alkaline phosphatase action and were proportionally lesser than wild type. Homozygous altered mice showed anomalous gait and severe skeletal anomalies, including variably reduced and twisted limbs, deformed or flattened ribs and scapulae, and late ossification of tail, snout, and pelvis. Bones of homozygous variants were also brittle and vulnerable to spontaneous fractures with developing callus [118].

n. Type XX OI (MESD: OMIM 607783)

The MBTPS2 gene is located on the 15p25.1 chromosome, comprising of 3 exons associated with autosomal recessive OI type XX. The individuals with type XX OI have blue sclera, dwarfism, joint contractures, hearing loss, and scoliosis. Moreover, the patients have progressive anomalies of bone complication categorized by osteopenia and few patients have died from respiratory failure [119]. MESD gene translates an ER chaperone protein for the recognized wingless associated integration site signifying receptors LRP5 and LRP6. Because full lack of MESD gene produces embryonic lethality in mice, we assumed that the OI related alterations are hypomorphic alleles since these alterations happen downstream of the chaperone action domain but upstream of the ER maintenance domain [119]. The gene recognized in the mesoderm development (MESD) removal break on mouse chromosome 7, is important for the requirement of embryonic polarization and mesoderm initiation. They identified that the modeling and cell distinction faults detected in MESD removal homozygotes lead to only damage of the Mesdc2 gene and it is renamed as MESD gene [120]. The researcher explained that Boca an evolutionarily preserved gene in Drosophila melanogaster (fruit fly) that translates an ER protein homologous to the mouse Mesdc2 protein. They revealed that Boca is particularly essential for the intracellular operating of partners of the LDLR family. Two LDLRs in flies, which are essential for wingless sign transduction, and yolkless, which is

required for yolk protein approval during oogenesis, were observed to involve Boca work [121].

3.3. X-linked recessive OI

a. Type XIX OI (MBTPS2: OMIM 300294)

The MBTPS2 gene is located on the Xp22.12 chromosome, comprising of 7 exons associated with X-link recessive OI type XIX. Homozygous or compound heterozygous mutation in MBTPS2 gene characterized by prenatal crakes and generalized osteopenia, dwarfism, scoliosis, skeleton deformity, and marked anterior angulation of the tibia. In the Golgi apparatus membrane, membrane-bound transcription factor protease, site 2 (MBTPS2) is located where it cuts intricate ER stress response substrates consisting of CREB3L1/OASIS, ATF6 and sterol regulatory element-binding alpha protein (SREBP). A novel missense variant in MPTBS2 that affected the notion that is necessary for protease catalytic purpose formed mild or severe X-linked recessive form of OI in two autonomous families. Compact CREB3L1/OASIS cleavage and reduced LH1 levels were seen by OI patient osteoblasts in a similar study, consistent with lower helical lysine hydroxylation levels (K87) and elevated LP/HP ratios [122].

4. MANAGEMENT AND TREATMENT OF OI

When the analysis of the OI has occurred and the suffered individuals should be checked by the multidisciplinary group. This team has performed a significant role in the treatment of OI in children and young people. Among these most of the individuals have not only recurrent fractures and severe bending abnormalities of long bones, leg joints, and connective tissue related complications. There is no proper treatment for OI because genetic involvement cannot be treated directly. But however, the symptomatic cure options are present and are used according to phenotypic disease severity [6].

4.1. Drug therapy

Bisphosphonates (BPs) are non-hydrolyzable chemical substances of pyrophosphate (Licata, 2005). BPs (oral alendronate, intravenous (IV) pamidronate) beneficial, which reduced fracture risk and better the minerals mass of bones and their tendency to decrease the osteoclastic resorption of bone in affected children [123]. BPs have decreased the chance of fracture frequency in children up to 100% [124]. However, most of the severely affected individuals get the IV BPs to enhance the levels of the minerals of bones and decrease the chance of fractures [6]. IV BPs are the new first cure for babies suffered from acute to severe OI. BPs improve the mass of the minerals of bones and size in kids with OI [125]. In growing children, IV cure also improves and strengthens the vertebral column who is suppressed by fractures. It is indicated that the BPs treatment is more effective in children as compared to the adults [126]. BPs do not play role in the formation of bone impairment but only enhance the cortical width in affected children [127]. In children suffered from OI, oral risedronate enhance the bone minerals mass and exist to be seen with reducing clinical fractures [128]. Fractures have been documented in affected children cured with BPs [129,130]. The osteonecrosis of the jaw has not present to be a serious complication in affected babies cured with BPs [131,132]. Although the increase in bone minerals mas have been documented during this cure, fracture findings are ambiguous [133].

4.2. Growth hormone therapy

Growth hormones have been attributed to the anabolic actions of the bone. The randomized controlled clinical trial (RCCT) analysis of the effect of a collected cure of BPs (Neridronate) and growth hormone in babies with severe to mild OI has been reported [134]. Some of the researchers' findings show that if the selection of BPs (Neridronate) and growth hormone will speed up the bone metabolism of OI affected infants, who are already healed with BPs, more (Neridronate). The activity of the combination drug improved the mass of bone minerals at the lumbar spine as well as increased enough in the preserved region and wrist [135]. Some researcher documented that the collection of recombinant growth hormone and BPs is under examination yet and advantageous for types I, III and IV OI, to enhance the direct development, the affected individuals are not endogenously growth hormone inadequate [134]. The hormone has the below types.

a. Teriparatide

Teriparatide (PTH1-34) is an anabolic agent which regulates the synthesis of bones and ultimately the resorption of bones [136]. The previous findings of OI patients revealed to enhance the bone minerals mass treated with teriparatide drugs [137,138]. Currently, a randomly experimental works on teriparatide drug in OI patients indicate to enhance the bone minerals mass and strengthen the vertebral column [139]. In moderate type I OI, the advantageous features of the medication are indicated, but not in chronic OI types III and IV. Many other studies have revealed a positive action on bone mineral mass in early menopause ladies with a statistically significant 3.5% enhance the bone mineral mass of the lumbar spine. Moreover, new studies are required to identify that the Teriparatide drug treatment is more valuable as compared to the treatment with BPs and other anti-resorptive in adult patients. It is not beneficial for babies because it causes bone carcinoma [138].

b. Denosumab

Denosumab is a nuclear kappa B ligand receptor activator monoclonal antibody that decreases bone resorption while raising the mass of bone minerals and decreases fractures in women with postmenopausal osteoporosis and decreases bone risk in OI patients with bone-caused carcinoma. This medication could be a sign of potential OI therapy [139]. A study was conducted in Germany on four affected children with type VI, enhanced the bone minerals mass, mobility, and well-established the shape of the vertebral column after the use of denosumab drug. The beneficial aspects of this study revealed that will lead to being safe [139]. Another study is also reported in two children treated by the denosumab use, these two children were suffered from OI caused by a mutation in genes like COL1A1 and COL1A2. Denosumab drug has been documented to produce hypocalcemia and hypophosphatemia in babies with abnormal bones. There was recover hypercalcemia after preventing the denosumab drug [140].

4.3. Surgical therapy

The common surgical operation for OI patients is "rodding" made of metal kept in long bones of arms and legs. This surgically fitted rod will lead to the strengthening of bones as well as avoiding fracture. The surgical treatment is mostly achieved to accurate anomalies and to decrease the bone softness, which prevents complicate bowing and to set the phenotypic condition of the patients. This method is also the best result of otosclerosis in which the patient did the stapedectomy (removal of steps) surgically [141]. Surgically fitted metal rod in the lower leg of the long bones revealed to perform the

proper function and ambulation in affected children of OI [142,143].

The adjustment of forearm abnormalities with rodding has also treated functional capability in affected children of OI assessed by the pediatric assessment of infirmity inventory [143]. Telescopic metal rods are mostly used in pediatric affected children facilitating for vertical height gain, but non-telescoping metal rods have used successfully. In a Danish experimental containing 9 children, who suffered a total of 16 surgical techniques with intra medullar metal rods, the maintenance of abnormalities in the lower legs reduced the ratio of fractures and facilitated highly previously non-ambulatory patients to walk [143]. Similarly, in Italy, the 29 patients with OI have recorded a mean age of 8.0±8.3 years. Of the 245 measures completed, 166 were for 110 fractures and 79 were for adjustment of abnormality. General surgical problems relating to fractures cure were non-union or delayed union 11.4%, malunion 5.7%, and transplant loosening 6.1% respectively [144]. Surgically treated intramedullary metal rodding of the lower leg bones have been revealed to recover the function and ambulation in affected children with OI [142,143]. Moreover, two researchers doctor also correct the deformity in 44 cases of OI with frequent fractures from 1989 to 2003. Among these 9 non-unions were faced in 8 patients. So, it is considered that non-union was frequent in OI patients [145]. Proper caution should be stressed in choosing the exact fixation of fractures and surgical remedies. Surgery may cause the long leg bone to be reshaped, but due to deformities in the soft tissue, simple healing is limited. Hearing damage may also be recovered by surgery. Patients are also prescribed to perform mild physical exercise such as cycling and water walking, etc [146].

4.4. Physical therapy

The aim of medical treatment is to relieve pain and fractures and to promote versatility. Physical therapy or therapy is especially necessary in infants to increase weight-bearing and decrease fractures, and to enhance strength and endurance during fracture improvement. Physical therapy is a procedure that may require the improvement of deltoids, biceps, and lower muscles such as gluteus maximus, gluteus medius, and trunk extensors that are necessary. Many children may require walking aids or wheelchairs. In order to sustain daily life activities, clinical care may be needed [2].

5. CONCLUSION

OI is a heterogeneous group of phenotypic and molecular diversity. In molecular diversity, groups of genes involved, a mutation in these genes causes impair production of type I collagen resulting in abnormal growth synthesis with reducing bone mass density and increase the risk of fractures. 90% of OI are produced by the mutation in type I collagen. Total of 20 genes that are involved in OI type I to type XX. Among these, 5 genes are autosomal dominant, and the remaining 15 genes are autosomal recessive and X-linked recessive. It is a curable pediatric syndrome and does not publish local data with respect to their therapy in children with OI in Pakistan. This review will provide in-depth knowledge to the concerned pediatricians, researchers, and family physicians for the preliminary assessment and management of OI in children. At present, experimental approaches have been studied, such as bisphosphonates, growth hormone, and gene therapy. Treatment with cyclical bisphosphonate has a positive impact on the rate of fracture, bone mineral density, agility score, and episode of pain. Nowadays surgical therapy is also valuable to some extent. Moreover, this study would also give careful management policy, combat against diseases, and a better understanding of OI.

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NA

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