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CLINICAL GENETICS OF HUMAN OSTEOGENESIS IMPERFECTA (OI): AN UPDATED REVIEW

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Abstract

The hallmark of Osteogenesis imperfecta (OI) is a predisposition to bone fractures, which can range in severity from somewhat increased fracture frequency to birth traumas. In 1788, OI was first described scientifically. Since then, the adoption of bisphosphonate therapy, the identification of abnormalities in collagen type I biosynthesis as the primary cause of most cases of OI, and the classification of OI into four categories (the "Sillence

classification") have all been significant turning points in the research and treatment of OI. Additionally, over the last five years, it has become evident that OI is a collection of diverse disorders, with 10% of cases thought to be caused by causative recessive variants in the 21 known genes and 90% of cases thought to be caused by causative dominant variants in the *COL1A1* or *COL1A2* genes. This review aims to highlight the current knowledge about the clinical, genetic and molecular analysis of the OI types has been presented comprising 23 genes with different location on chromosomes. Concerned family doctors, researchers and pediatricians may find this review useful in assessing and treating OI in children at the outset. It also provides a summary of the complex molecular mechanism responsible for the OI and might be helpful in genetic counseling and rapid genetic identification.

Key words: Molecular analysis, Osteogenesis imperfecta, Brittle bone disease, Autosomal recessive, Genetics variants.

Introduction

Osteogenesis Imperfecta (OI) is a diverse group of connective tissue anomalies with wide range of clinicals considered mainly by bone fragility or "brittle bone disease" (Figure 1). Patients with OI have clinical features that may range from mild symptoms to severe bone deformities and neonatal lethality. Numerous approaches for the classification of OI have been published. The Sillence classification is the most commonly used (Botor et al., 2021). The persons with OI may also suffer from other phenotypes like brittle teeth, blue sclera, hearing loss, reduced respiratory function, and cardiac valvular regurgitation (Forlino et al., 2016). The estimate incidence of OI is 1/15,000 to 1/20,000 of live births respectively. Five kinds of the disorder are usually distinguished, ranging from mild (type I) to lethal (type II). Kinds III and IV are severe forms allowing after the newborn period, while type V is considered by mild to adequate clinicals with calcification of interosseous tissues. In maximum cases, there is a decrease in the manufacture of normal type I collagen or the production of anomalous collagen because of changes in gene responsible for the type 1 collagens. Furthermore, alterations in genes caused in col I synthesis and processing as well as in osteoblast variation have been recorded (Botor et al., 2021). It is form by variation in genes like *COL1A1* and *COL1A2* responsible for the production collagen type 1. However, these mutated genes cause defective collagen effects on bones rather than other organs of the body. It is known that 90% of OI disease is formed by dominant autosomal genes like *COL1A1* or *COL1A2*, while remaining 10% of the disease is due to 08 autosomal recessive genes like *WNT1, FKBP10, CRTAP* and *SPARC* etc. Structural and qualitative faults are strongly linked with more severe clinical than quantitative faults. Collagen is

the chief protein in the extracellular matrix of connective tissues composed of three polypeptide chains that arrange in triple helix by glycine molecule (Forlino et al., 2016). In contrast, haploinsufficiency of *COL1A1* decreases the manufacture of structurally normal collagen, leading to the incidence of the mildest form of OI. Alteration in *COL1A2* will lead to clinicals ranging from mild to severe OI. Homozygous null mutations of *COL1A2* result in phenotypes ranging from mild to severe OI, while haploinsufficiency of *COL1A2* produces a normal clinicals. Furthermore, another rare autosomal dominant pathogenic variant in *IFITM5* (Hoyer-Kuhn et al., 2016). This variant causes the inhibition of differentiation and mineralization in bone (Marom et al., 2016).

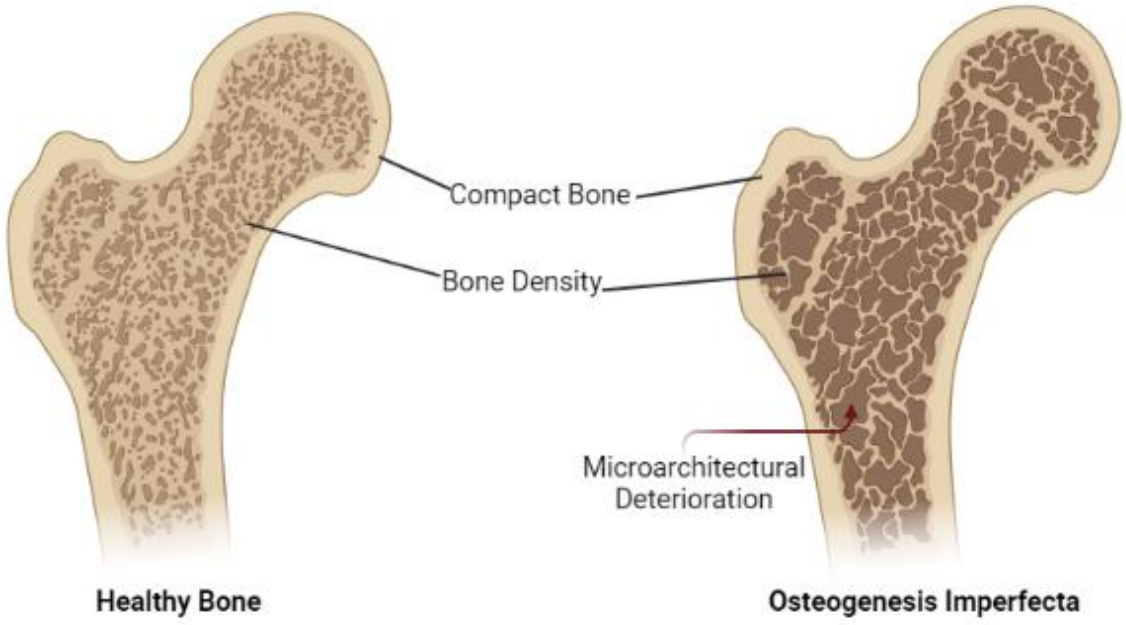

Figure 1: Healthy and Osteogenesis bone comparison

With a rise in the discovery of the number of pathogenic variants is responsible for causing OI and classified into XXIII OI type to date. However, even within the similar genetic variants, numerous clinicals are recorded. Therefore, it is difficult to compare them genetic classification with the Sillence classification (Marom et al., 2016). Skeletal anomalies comprise more than 450 disorders (Mortier et al., 2019). OI is the second most frequent type of severe skeletal anomalies. The essential differential analyses are thanatophoric dysplasia and achondrogenesis, which also comprise prenatally fatal type. Thanatophoric dysplasia is the frequent type of disorder, which is categorized by

enormously short limbs, small chest, macrocrania, frontal bossing, cloverleaf skull, and normal mineralization without fractures (Vanegas et al., 2018). Once imaging modalities reveal a prenatal analysis of OI, laboratory examinations are accessible to the parents. Genetic counseling is strongly suggested before undertaking any test (Zhytnik et al., 2020). When a fetus is identified with fatal OI, removal of fetus is one of the options. However, globally, 40% of women are lived in country, where fetus removal is banned or limited (Bernabe-Ortiz et al., 2009).

The presently obtainable treatments try to avoid fractures, (Figure 2), control signs and rise bone mass. Normally used medicines in OI therapy are bisphosphonates, Denosumab, synthetic parathyroid hormone and growth hormone for children treatment. The most common and main demerits of these treatments are their comparatively weak effectiveness, absence of special effects in some patients or cytotoxic side effects. Investigational methods, mainly those based on stem cell transplantation and genetic engineering; appear to be promising to develop the therapeutic effects of OI (Botor et al., 2021). Furthermore, other medicine such as Fresolimumab (GC1008) antibody that prevents TGF-β, earlier used against carcinoma, but recently in scientific trials to prove its protection and efficacy used in OI therapy (Chitty et al., 2021). In other study, it is reported that inhibition of TGF-β-regulated genes expression in comeback to Fresolimumab in a study designed on sclerosis patients. The drug needs more studies but appears capable for the real therapy of OI in the future (Rice et al., 2015).

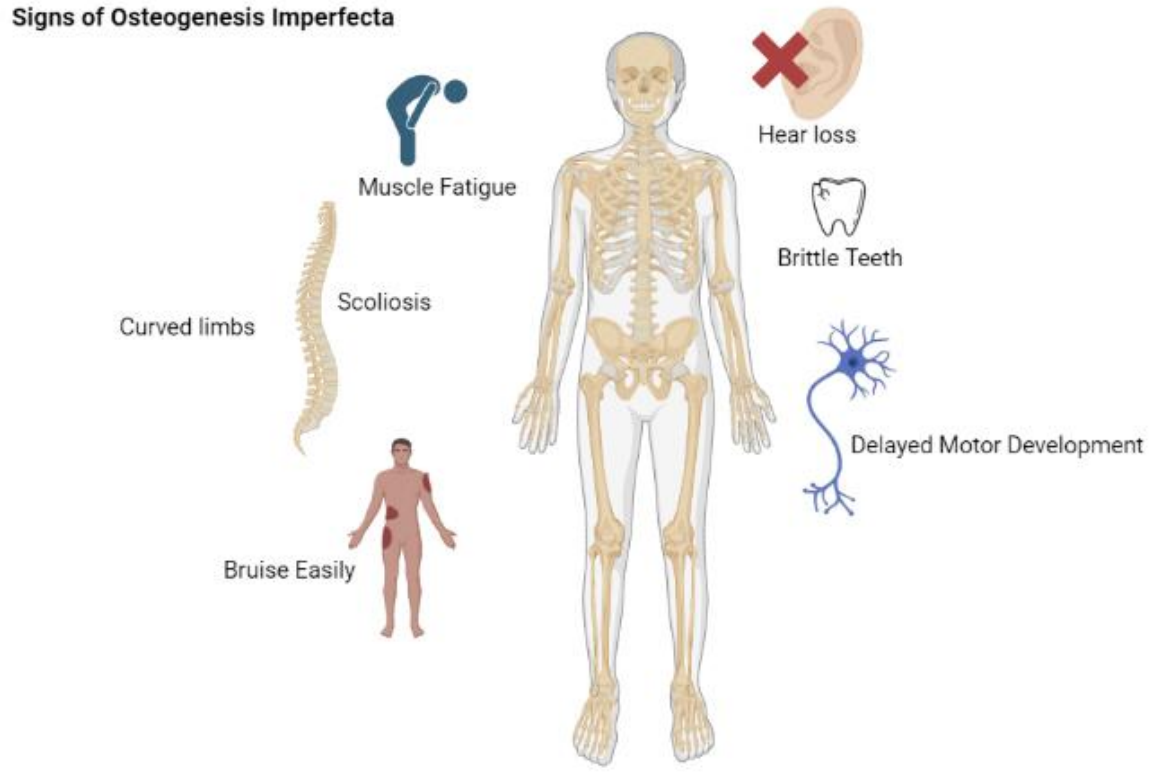

Figure 2: Signs of Osteogenesis Imperfecta (OI).

Table 1: *Current classification of OI.*

Location	Phenotype	Inheritance	Phenotype MIM number	Gene/Locus	OMIM	Clinical description
1p34.2	OI type VIII	AR	610915	*P3H1* (*LEPRE1*) OI,8	610339	Progressive abnormalities, white sclera, mineralization, severe rhizomelia, dwarfism, growth deficiency and extreme bone fragility.
3p22.3	OI type VII	AR	610682	*CRTAP*, OI,7	605497	Bones fragility, dentinogenesis imperfecta (DI) absent, blue sclera, shortening of femur and humorous, ligamentous laxity and hearing impairment.

5q33.1	OI type XVII	AR	616507	*SPARC*, OI,17	182120	Blue sclera, bowing of spine (scoliosis), hear impairment, dwarfism, joints complications (contractures), DI, respiratory problems, skeletal abnormality at birth but developed progressively and severe bone fragility.
6q14.1	OI type XVIII	AR	617952	*TENT5A* (*FAM46A*) OI,18	611357	Congenital bending of long bones, blue sclera, wormian bones, vertebral failure and multiple fractures in the first years of life.
7q21.3	OI type II	AD	166210	*COL1A2*, OI,2	120160	Deformities of ribs, vertebrae, short stature, stiffness of long bones lead to crakes, lungs failure, respiratory complications, blue sclera, pulmonary hypoplasia, central nervous system, DI and skull is delicate and large.
7q21.3	OI type III	AD	259420	*COL1A2*, OI,3	120160	Blue, grey or whitens sclera, DI, progressive abnormality, scoliosis, shortening and bending of long bones, hearing impairment, triangular faces and pulmonary complications.
7q21.3	OI type IV	AD	166220	*COL1A2*, OI,4	120160	Hear loss, DI, multiple fractures, different level of abnormality, change of sclera color, long bone bending, cranial settling, joint laxity and scoliosis.
8p21.3	OI type	AR	614856	*BMP1*,	112264	Severe bones deformities,

	XIII			OI,13		blue sclera, severe growth deficiency, bone fragility, recurrent fractures, osteopenia and wormian bones.
9q31.2	OI type XIV	AR	615066	*TMEM38B*, OI,14	611236	Severe multiple fractures, osteopenia with normal hearing, dentition and sclera. Fractures mostly occurred at the age of 06 years old
11p15.5	OI type V	AD	610967	*IFITM5*, OI,5	614757	Fore arm interosseous membrane which starts to radial head mobility and callus development (hyperplastic) and long bone fractures can lead in a very hypertrophic callus. Temperately bending and patients show mild to severe bone softness.
11p11.2	OI type XVI	AR	616229	*CREB3L1*, OI,16	616215	Severe demineralization, reduced ossification of skull, blue sclera, multiple fractures long bones, ribs, osteopenia and recurrent fractures.
11q13.5	OI type X	AR	613848	*SERPINH1* (*CBP2*) OI,10	600943	Bones deformities with fractures, DI, osteopenia, blue sclera, renal stones, triangular face, relative macrocephaly, thin ribs, micrognathia, and short bowed limbs.
12q13.12	OI type XV	AR	615220	WNT1, OI,15	164820	Bone deformities with recurrent fractures, dwarfism, reduce bone mass density,

						bending of upper and lower limb, multiple vertebral compression and muscle hypotonia.
12q13.13	OI type XII	AR	613849	*SP7* (*OSX*) OI,12	606633	Recurrent fractures, mild bone abnormalities, late discharge of teeth, lack of DI, white sclera, bowing of lower limbs short stature, osteoporosis and hearing loss.
15q22.31	OI type IX	AR	259440	*PPIB* (*CYPB)* OI,9	123841	Blue sclera, short stature, reduces bone mass density with many fractures, perinatal lethality to moderate severity without rhizomelia and severe deformity of the long bones.
15q25.1	OI type XX	AR	618644	*MESD* (*MESDC2*) OI,20	607783	Dwarfism, blue sclera, joint contractures, hears loss, scoliosis, respiratory failure and progressive anomalies of bone with osteopenia.
17p13.3	OI type VI	AR	613982	*SERPINF1* (*PEDF*) OI,6	172860	Scale of fish appearance of bone, low mineralization, osteoid accumulation indicates a mineralization complication similar to osteomalacia, fractures of long bones and severe vertebral compression fractures.
17q21.2	OI type XI	AR	610968	*FKBP10*, OI,11	607063	Severe progressive fractures, distortion, congenital joint contractures, Kuskokwim syndrome, short stature with

						osteopenia, Bruk syndrome and osteoporotic vertebrae.
17q21.33	OI type III	AD	259420	*COL1A1*, OI,3	120150	Blue or grey sclera at embryonic stage, DI, progressive abnormality, scoliosis, hearing impairment, triangular faces and respiratory complications
17q21.33	OI type II	AD	166210	*COL1A1*, OI,1, OI,2	120150	Ribs, vertebrae, anomalies, dwarfism, bending of long bones causes fractures, lungs failure, pulmonary hypoplasia, DI, and reduce skull.
17q21.33	OI type I	AD	166200	*COL1A1*, OI,1, OI,2, OI,3, OI,4	120150	Number of fractures, collagen deficiency causes dental complications, development and size are slightly reduced, vertebral fractures cause scoliosis, blue sclera and hearing impairment.
17q21.33	OI type IV	AD	166220	*COL1A1*, OI,1, OI,2, OI,3, OI,4	120150	DI, hear impairment, dwarfism, multiple fractures, different level of abnormal change of sclera color, long bone bending, cranial settling, joint laxity and scoliosis.
Xp22.12	OI type XIX	XLR	301014	*MBTPS2*, (*S2P)* OI,19	300294	Prenatal fractures, generalized osteopenia, dwarfism, scoliosis, skeleton deformity and anterior angulation of the tibia.

3q24	BRSK2, OI	AR	609220	*PLOD2,* BRSK2 OI	601865	Short stature, pectus carinatum, osteopenia, congenital joint contracture (elbow, knees), bone fragility, clubfeet, platyspondyly and clenched hands with clasped thumbs.
7q22.1	OI type XXI	AR	619131	*KDELR2,* OI, 21	609024	Dwarfism, blue sclera, DI, thin ribs, pectus excavatum, reduce bone minerals density, wormian bones, scoliosis, coxa-vera, bowing of long bones, muscular hypotonia and neurological disorders.
22q31.2	OI type XXII	AR	619795	*CCDC134* OI,22	619795	Shot stature, blue sclera, pectus excavatum, severe bone fragility, multiple fractures, wormian bones, scoliosis, kyphosis, bowing of long bones and intrauterine fractures.
11q23.3	OI type XXIII	AR	620639	*PHLDB1 OI,23*	612834	Dwarfism, truncal obesity, blue sclera, osteopenia, bone fragility and fractures, platyspondyly, lumber lordosis, coxa-vera, bowing of limbs, broadening of wrist and neurological disorders.

Nosology of the OI

As a reminder of the differential diagnosis, nosology has also been useful for pediatricians, geneticists, radiologists, and other professionals. Its original structure in groups of illnesses with similar radiographic structures revealed the investigative approach of the clinical geneticist and even more, of the radiologist, to the osteochondrodysplasias. The enormous number of genes and gene products necessary

for proper skeletal development and growth serves as another example of the complexity of the human genome (Unger et al., 2023).

Type I OI (*COL1A1*)

The gene *COL1A1* is an autosomal dominant produced type I OI, positioned on chromosome 17q21.33 respectively (Swinnen et al., 2011). In OI type I patients there is no bone irregularity and a substantial variability in case of number of fractures, reported in the same family. Fractures usually produced when the children begin to ambulate. There may be slight teeth results (Forlino et al., 2011). The symptoms of the individuals associated with skeletal are vertebral fractures, which are not correlated with abnormalities, which can cause scoliosis. Except these, there are many defects of the individuals like blue sclera, hearing impairment loss showed in table 1. Although zebra fish has not appropriate for the valuation of bone growth and related disorder, few research have been emphasized its potential. The tetrapod's, the skull bone of the zebra fish develops directly consuming cartilage model However, the zebra fish cranial nerve crest performs same role as in the tetrapod's representing that the skull maximum part is of neural crest derived. The many other members of genes like hedgehog, runx, and dlx are control osteoblast variations in mammals and similar expression during zebra fish bone development (Sam & Dharmalingam, 2018). Total 55 (17.44%) mutations were reported in 61 families, among these 78 (17.44%) male patients and 61 (15.68%) female patient was recorded from different ethnic origion (table 2&3). The safety of intravenous bisphosphonates (IVBPs) has been studied for the osteoporosis therapy and reduces mineral density in children bone with spinal muscular atrophy (Nasomyont et al., 2019).

Type II OI (*COL1A1, COL1A2*)

Both *COL1A1, COL1A2* autosomal dominant genes are responsible for type II OI, located on chromosomes 17q21.33 (51 exons) and 7q21.3 (52 exons) correspondingly (Sillence et al., 1984). In utero stage of the individuals has deformities of ribs, vertebrae, short stature, and stiffness of long bones lead to skeletal fractures indicated in table 1. Moreover, any other indicators like failure of lungs, respiratory problems, blue sclera, pulmonary hypoplasia ultimately death central nervous system abnormalities and dentinogenesis imperfecta (OI) (Sam & Dharmalingam, 2018). The skull is usually very delicate and large. In dogs, OI is also present and indicate a well model for men OI than hereditarily modified mice because of their bigger body size and the successive similarity of automatic forces that perform on the skeleton. OI explained in different species of the dogs like Golden Retrievers, Beagles, Collies, Poodles, Norwegian Elkhounds and Bedlington Terriers, respectively. Two dog species, Golden Retrievers and Beagles, have been linked to an OI disease mutation in the *COL1A1* and *COL1A2* genes.

The genetic complications regarding OI have not explained in other members of the Canidae family (Forlino et al., 2011). In the Crtap KO mouse model of recessive pattern of OI indicated that type I collagen in the lung had similar complications as in the bone and skin (Dimori et al., 2020).

It is expected that change in genes other than those coding type I collagen are liable for about 15–25% of OI patients, with pathogenic alleles indicating different environmental distribution (Fernandes et al., 2020). The *COL1A1* re-sequencing of consuming DNA of four affected and four control Wiene dogs did not expose any disease concerned sequence polymorphism within the 51 coding exons and neighboring intron areas of the *COL1A1* gene (Drogemuller et al., 2009).

Types III & IV OI (*COL1A2*)

COL1A2 is an autosomal dominant gene present on chromosome 7q21.3 which causes OI types III & IV. Expressions of OI types III & IV in individuals can start in embryonic stage or by birth. It is comprised the blue, grey or whitens sclera (Marini et al., 2014), dentinogenesis imperfecta (DI) and caused to a progressive aberration and scoliosis. It also caused short stature, shortening, and bending of long bones, hearing impairment, triangular faces, respiratory and pulmonary problems (Forlino et al., 2016). Moreover, the other phenotypes in individuals like multiple fractures, cranial settling, and joint laxity indicated in table 1. The genes of the bone matrix containing *COL1A12* and *osn* display strangely alike expression models. Both genes in epidermis region are expressed of the zebra fish indicating the fin fold and connective tissue, but *osn* is expressed in the ear development. This general manifestation comparatively shows that their clarification is difficult, mainly with deep bones like Para sphenoid. The scientifically assessment of skeletal features of zebra fish models primary different variants in type I collagen of zebra fish containing *COL1A* (col1a1a, col1a1b*)* and *COL1A2* genes translating α1 and α3 chain respectively. Two knockout variants also involved (bmp1a, plod2) indicating severe OI in recessive pattern with faults in type I collagen assessing and cross linking (Gistelinck et al., 2016). During mutational analysis detected different abnormalities of skeletal phenotypes containing callus development, bending, and kinking of the ribs, deformity of the vertebral column, dwarfism, and craniofacial anomalies respectively (Hur et al., 2017). Moreover, a high preservation of develop programs in Osteogenesis between teleost's fish and mammals, the assessment of efficient gene and mechanism in zebra fish can produce relation to the human skeleton disease (Harris et al., 2014). In 25 families, total 23 (11.38%) mutations were reported, among these 48 (10.73%) male patients and 81 (20.82%) female patient was recorded from different ethnic origion (table 2&3).

Type V OI (*IFITM5*)

The autosomal dominant gene *IFITM5* contains on chromosome 11p15.5, with 02 exons, identified and mutated in gene, which produces many complications (Marini et al., 2013). The Type V OI common characteristics are calcification of the forearm interosseous membrane, which initates to radial head mobility and callus development (hyperplastic) and long bone fractures showed in table 1, which can lead in a very hypertrophic callus (Cho et al., 2012). Total 02 (0.99%) mutations were reported in 25 families, among these 48 (10.73 %) male patients and 81 (20.82%) female patient was recorded from different ethnic origion (table 2&3). Temperately Type V OI is bending and patients shows mild to severe bone softness. In mice, the *IFITM5* showed the bent bones by birth and after modified in adult stage. The shorter appendicular elements but not superficial influences on bone mass. Frequently, in this gene the human variants are produced by a single heterozygous variant mutation (c.-14C>T) in the 5′ end which shows the autosomal dominant OI type V (Tosi & Warman, 2015). In mice inherited the mutant *IFITM5*shows that the late mineralization, utero fractures and severe skeletal deformity, but perinatal bone mass could not be recognized due to perinatal lethality. Moreover, the mice legs have lacked growth deformities representing the foreleg and hindleg fractures as well irregularities in rib cage respectively (Lietman et al., 2015).

Classification of Autosomal Recessive OI

Type VI OI (*SERPINF1*)

The *SERPINF1* gene consists on 17p13.3 chromosome comprising 08 exons with autosomal recessive pattern (Balasubramanian et al., 2013). Children with type VI has showed alkaline phosphatase and scale of fish appearance of bone, studied beneath the microscope and low mineralization indicated in table 1 (Homan et al., 2011). During or by birth but slowly or with the passage of time shows severe abnormalities (Sam et al., 2018). Total 20 (9.90%) mutations were reported in 20 families, among these 30 (6.71 %) male patients and 13 (3.34%) female patient was recorded from different ethnic origion (table 2&3). Lacking in pigment of transgenic mice are to be epithelium-derived factor (PEDF) were first made by replacing exons 3 & 6 of *SERPINF1* gene containing of an internal ribosomal entry site, galactosidase genes and neomycin-resistance genes. Later it revealed that type VI OI produced by change in *SERPINF1* gene in human, this process was first simulated to create PEDF mice for the determination of learning the role of PEDF in bone and other tissues. The PEDF is mainly formed in the liver and at lesser levels in bone; it was assumed that PEDF levels may accurate the bone features in type VI OI. Furthermore, to drive man *SERPINF1* expression in mouse liver the helper dependent adenovirus (HDAd) was used, over-expression of PEDF did not progress the

bone feature in *SERPINF1* gene because mice regardless of returning biologically active PEDF serum levels (Rajagopal et al., 2016). It is renowned that the intraperitoneal inoculation of PEDF comprising microspheres clearly improved bone mass and moderately biomechanical parameters (Belinsky et al., 2016). Pathogenic change in *SERPINF1* will reveal to a recessive pattern of OI considered by low mineral density. There are enormous progresses in understanding the genetic basis of OI, but unfortunately, this has not been attended by comparable advancement in terms of therapy (Ralston et al., 2020). The usage of induced pluripotent stem cells (iPSCs) indicates another exciting method to OI treatment, newly fascinating the attention of scientists globally (Kim et al., 2019).

Type VII OI (*CRTAP*)

OI type VII in *CRTAP* gene is caused by alteration, which liked on 3p22.3 chromosome with 07 exon. The two allelic changes in pathogenic the *CRTAP* gene producing complete deterioration of protein function, which cause OI, type VII. It is predicted that 2% to 3% cases are due to change in *CRTAP* gene (Balasubramanian et al., 2013). The type VII, individual is clinical expression of bones abnormality, fragility, absence of dentinogenesis imperfecta (DI) and blue sclera. Moreover, shortening of femur and humorous showed in table 1 (Roughley et al., 2003), during or by birth show slowly or with the passage of time indicates severe abnormalities (Sam et al., 2018). It is documented that the hereditary reason of type VII OI in humans was strongly concerned to a shortage in *CRTAP* expression; a strain of homozygous *CRTAP* lacking mice was formed using a homologous recombination method (Fratzl-Zelman et al., 2010). It has been showed that the *CRTAP* mice correctly model OI in humans, as they have an oddly high level of mineral and improved mineral densities in their bones associated to wild type mice, (Fratzl-Zelman et al., 2010). Other features noted in *CRTAP* in mice comprise a progressive severe kyphoscoliosis, low bone density and cartilage anomaly (Glorieux et al., 2014). However, the *CRTAP* mice showed to have a fewer severe form of the disorder than is present in maximum humans (Glorieux et al., 2014; Marini et al., 2010). In 16 families, 14 (6.93%) mutations were reported, 36 (8.05%) male patients and 22 (5.65%) female patient was recorded from different area of the world (table 2&3).

Type VIII OI (*P3H1*)

Type VIII is a recessive autosomal inheritance that underlies on chromosome 1p34.2 containing 14 exon respectively and encodes Prolyl 3-hydroxylase 1 protein. Children with type VIII OI have progressive abnormalities, white sclera, mineralization of skeleton, severe rhizomelia indicated in table 1, and dwarfism (Xu et al., 2020). A technique of homologous genetic recombination in 2010 was used to generate a *P3H1* knockout

mouse by targeting exons 1 & 3, respectively. The heterozygous *P3H1* mice did not shows an OI features, but homozygous *P3H1* mice showed suggestively smaller body size, lesser mineral density in the skull and long bones, progressive kyphoscoliosis and shorter femora that had reduced stiffness and failure load associated to wild type littermates (Vranka et al., 2010). Moreover, knockin mice comprising one amino acid change of the *P3H1* catalytic region, this eradicated enzymatic action while maintaining the capability to linked with *CRTAP* and form the *P3H1* complex, resulting osteopenia without apparent influence on mouse growth (Homan et al., 2011). Personalized iPSCs establish a precious cell type for use in extra treatment. Until now, iPSCs have been achieved from peripheral blood mononuclear cells and used for OI type I therapy (Fus-Kujawa et al., 2021). Pathogenic change in *P3H1* will reveal to a recessive pattern of OI considered by low mineral density. There are enormous progresses in understanding the genetic basis of OI, but unfortunately, this has not been attended by comparable advancement in terms of therapy (Ralston et al., 2020). Total 02 (0.99 %) mutations were reported in 02 families, among these 08 (1.78%) male patients and 55 (14.13%) female patient was recorded from different ethnic origion (table 2&3).

Type IX OI (*PPIB*)

Type IX OI is a recessive autosomal inheritance that is located on chromosome 15q22.31 containing 05 exon only. The type IX clinical manifestation is shown resemblance to the types II or III OI without dentinogenesis imperfecta (DI). The unique features of type IX are included such as severe abnormalities, blue sclera, short stature, reduce bone mass density with many fractures showed in table 1 are seen (Morello et al., 2006). The heterozygous *PPIB* mice that were made using this method did not show any signs of OI and were bred to create *PPIB* sibling (Choi et al., 2009), which instead show signs of OI, comprising reduced body size and weight, less bone mineral density and volume, progressive kyphosis, reduced skin stiffness and enhanced laxity. Although the clinical features documented in *PPIB* mice is low severe than in humans, it is indicated a suitable model of type IX OI (Choi et al., 2009). Total 03 (1.48%) mutations were reported in 03 families, among these 01 (0.22%) male patients and 05 (1.28%) female patients were recorded from different ethnic origion (table 2&3). Hearing loss is an additional skeletal manifestation of OI; this has been mainly defined in patients with dominant *COL1A1/COL1A2* and recessive farm of OI and in mouse models of OI (Machol et al., 2020). Severe short stature is also caused in OI and particularly affects the individuals with OI type III or any other. This aspect of the disorder is not well calculated, but it negatively influences the quality of life of these patients (Barber et al., 2019). Bisphosphonate can be directed to children younger than 24 months old with net

results on reduced fractures rates and improved patient mobility. Further, studies have revealed a reduced fracture risk for children without change of linear growth (Palomo et al., 2015). A new therapy such as anti sclerostin antibody, which leads to reduce the development in osteoporosis and has revealed an exciting advantage in OI (Sinder et al., 2016). An extra research was accomplished on a single human fetus offering an OI disorder. Allogeneic fetal mesenchymal stem cells were moved in utero, and the cells were exposed to engraft and differentiate into bone even when the recipient was immune competent (Hoyer-Kuhn et al., 2016).

Type X OI (*SERPINH1*)

Type X OI is a recessive autosomal inheritance condition produced by change in *SERPINH1* gene located on 11q13.5 chromosome comprising 05 exons. Common characteristic of type X OI are multiple bones deformities and fractures, dentinogenesis imperfecta (DI), generalized osteopenia showed in table 1 and blue sclera (Christiansen et al., 2010). Total 2 (0.99%) mutations were reported in 02 families, among these 3 (0.67 %) male patients without female patients ratio was recorded from different ethnic origion (table 2&3). Moreover, the individuals with type X have severe abnormalities and renal stones (Sam et al., 2018). It is documented that mutation in *SERPINH1* in dogs with OI delivers an appreciated model for human medicine and a fifth OI gene in addition to *COL1A1, COL1A2, CRTAP* and *LEPRE1* respectively. Drogemuller and his colleague reported missense mutation (c.977C.T, p.L326P) in *SERPINH1* gene in Dachshunds (Wiene dog) (Drogemuller et al., 2009). It was also documented that *SERPINH1* fibroblasts create abnormally thin and branched collagen type I fibres (Sam et al., 2018). All dogs bearing OI disease showed homozygosity at both tested microsatellites and all genotyped parents had one copy of the disorder concerned haplotype. The researcher showed variants in the canine *SERPINH1* gene might be liable for the OI features (Drogemuller et al., 2009). Essentially, the disorder in these circumstances is permanently systemic, because fibroblasts in other tissues and body systems also manufacture anomalous type I collagen such as in the eyes, lungs and heart valves respectively. Alterations disturbing genes dissimilar to type I collagen production seem to have harmful effects on the difference and function of osteoblasts, which eventually consequence in significantly reduced bone development and thus brittle bones (Dimori et al., 2020). The modern research on muscle function in oim/oim mice exhibited mitochondrial malfunction in the gastrocnemius muscle, with reduced mitochondrial citrate synthase action and respiration amounts (Gremminger et al., 2019).

Type XI OI (*FKBP10*)

The autosomal recessive gene *FKBP10* is located on 17q21.2 chromosome comprising 10 exon was recognized. It produces the severe progressive fractures, distortion, congenital joint contractures, and Kuskokwim syndrome showed in table 1 respectively. It interprets a protein called as *FKBP65* protein with molecular weight of 65kDa respectively (Shaheen et al., 2012). Total 17 (8.41%) mutations were reported in 40 families, among these 37 (8.27 %) male patients and 56 (14.39%) female patient was recorded from different ethnic origion (table 2&3). The anomalous development of craniofacial has been recognized in all OI types (Reznikov et al., 2019). Dental anomalies like dentinogenesis imperfecta (brittle or discolored teeth), missing teeth, ectopic teeth, and dental malocclusion are frequent in OI and are more common in the severe types of OI. These anomalies are strongly linked with efficient restrictions and effect of quality of life (Fiscaletti et al., 2018). The European conditional mutagenesis allele was designed to clarify the function of *FKBP10* in mice. In the early construction of heterozygotes of the mice, the clinical feature of OI was not noted. But, homozygotes mice, got from breeding showed late growth and as well as descending facing forelimbs, brittle tissue, flattened facial structures, endoplasmic reticulum (ER) enlargement produced by gathering of anomalous procollagen chains in the ER, and perinatal decease. On the other hand, the type XI OI did not showed perinatal decease, the effect of alteration has on the ER and collagen creation is phenotypically alike to *FKBP10* in mice. Opposing the human variant in *FKBP10*, mice showed the perinatal decease due to embryonic lethality, perhaps due to vasculature faults, generalized tissue brittleness or poor lung function. In this respect, a conditional knockout mouse model for *FKBP10* would be beneficial to control the bone and tendon roles of *FKBP10* elimination in postnatal mice (Lietman et al., 2014). Same effects were recorded in individuals with postmenopausal osteoporosis therapy with Romosozumab, which enhance the bone mineral density and detected in the lumbar vertebrae, femoral neck and hipbone (Ebina et al., 2020).

The autosomal recessive gene *PLOD2* is located on 3q24 chromosome comprising 20 exon was recognized. It produces Short stature, pectus carinatum, osteopenia, clubfeet, platyspondyly and clenched hands with clasped thumbs shown in table 1. Five families of the Egyptian origion were screened and identified mutations, c.1856G>A p.Arg619His, c.1559dupC p.Val523Cysfs∗ 7 and (c.2122-2A>G in *PLOD2* gene responsible for the Bruck syndrome (BS). Total 05 (2.47%) mutations were reported, among these 06 (1.34%) male patients and 01 (0.25%) female patients were recorded from different ethnic origion (table 2&3). BS is inherited disorder defined by congenital contractures of the large joints (elbow, knees) and bone fragility, resulting in fractures

starting in infancy or early childhood. It showed that collagen in bone and collagen synthesized by cultured skin fibroblasts in patients with BS showed none of the changes commonly found in OI. They reported that the molecular defect underlying BS is a deficiency of bone-specific telopeptide lysyl hydroxylase, which results in aberrant crosslinking of bone collagen (Puig-Hervas et al., 2012).

Type XII OI (*SP7*)

Type XII OI is a recessive autosomal manner, caused by change in the *SP7* gene located on 12q13.13 chromosome containing 02 exons. The individuals with type XII have categorized by frequent fractures, mild bone irregularities, osteoporosis, late discharge of teeth, and lack of dentinogenesis imperfecta (DI), white sclera and normal hearing showed in table 1. Furthermore, bowing of lower limbs and short stature are also stated (Lapunzina et al., 2010). The OI are recessively pattern of inheritance with severe forms of the disease, which are caused by change in genes that influence osteoblast differentiation comprising *SP7*, *WNT1*, and *CREB3L1* respectively. There are enormous progresses in understanding the genetic basis of OI, but unfortunately, this has not been attended by comparable advancement in terms of therapy (Ralston et al., 2023). Total 01 (0.49%) mutations were reported in 01 family, among these 01 (0.22 %) male patients and (0.00%) female patient was recorded from different ethnic origion (table 2&3). One primary technique to make a *Sp7* null mouse elaborate using a homologous recombination of embryonic stem cells to make non-phenotypic heterozygous in *Sp7* mice. However, *Sp7* null progeny got from *Sp7* couplings all deceased within 15 minutes of birth resulting difficulty breathing, and showed severe limb abnormalities. The secondary technique used the Cre/Lox structure to make conditional *SP7* knockout mice with Col1a1, which was planned to deactivate *SP7* without perinatal lethality. The *COLIA1* mice exposed reduced trabecular bone mineralization, as well as osteopenia and cortical bone weakening. Although both techniques occurred before *SP7* was associated to OI in humans, correspondingly (Baek et al., 2010).

Type XIII OI (*BMP1*)

OI type XIII is a recessive autosomal inheritance, produced by change in *BMP1* gene located on chromosome 8p21.3 with 16 exons (Martinez-Glez et al., 2012). It encodes the protein bone morphogenetic protein 1 (osterix) responsible for the osteoblast differentiation. The children with type XIII have severe bones deformities, blue sclera and severe growth deficiency is reported (Marini et al., 2014). They have also recurrent bone fractures and hyperextensible joints with high bone mass density showed in table 1 (Sam et al., 2018). The improvement of stem cell transplant therapy, there is a growing chance that the therapy of OI could be happening during pregnancy. Primary treatment

may increase the consequence of stem cell transplantation, as there might be a reduced level of anomalous collagen protein that needs replacement (Gotherstrom et al., 2020). The central disadvantages of the invasive tests are bodily uneasiness for mothers and enhance the chance of miscarriage. Therefore, a new research indicated that the amniocentesis are not related and enhance the risk of miscarriage in women passing through these events (Salomon et al., 2019). *BMP1* variation in zebra fish called as frilly fins (Frf), produces a ruffled larval fin, reduced body axis, and deformed craniofacial bones, vertebrae and short ossification and bone density. Frf was formed by missense changes in *BMP1* and controlled to osteoblasts showing an extra cuboidal structure than wild type fish (Asharani et al., 2012). Total 08 (3.96%) mutations were reported in 07 families, among these 72 (16.10%) male patients and 11 (2.82%) female patient was recorded from different ethnic origion (table 2&3). *BMP1* has also been revealed to show protease action on extracellular matrix (ECM) proteins *BMP1* mice embryos exposed short ossification of the cranium, parietal and interparietal bones of the skull but no distinct anomalies in the axial or appendicular skeleton. The absence of a robust skeletal features in *BMP1* mice are probable due to residual C-proteinase action of tolloid as immediate removal of *BMP1* and in perinatal mice suggestively decreased bone mass, length, and biomechanical characteristic due to improved bone turnover (Uzel et al., 2001; Muir et al., 2014).

Type XIV OI (*TMEM38B*)

OI type XIV is a recessive inheritance produced by the change in *TMEM38B* gene located on 9q31.2 chromosome comprising 06 exons. The diagnostic characteristic of type XIV patients has severe multiple fractures, osteopenia, with normal hearing, dentition, and sclera indicated in table 1. Fractures mostly happened at the age of 06 years old (Shaheen et al., 2012). In 16 families, total 03 (1.48%) mutations were recorded, among these 28 (6.26%) male and 22 (5.65%) female patients were reported from different ethnic origion (table 2&3). The gene *TMEM38B* translates the TRIC-B, which play vital role in intracellular calcium signaling. Complication in TRIC-B produce the imperfect calcium signaling in bone cells causes type XIV disorder (Marini et al., 2014). In mice, the *TMEM38B* variation resulted mice die quickly because of after birth due to lung deformities after birth. During birth, these mice show important damage of bone mineralization. Primary calvarial osteoblasts from mice existing decreased mineralization despite a rise in collagen protein gathering in the endoplasmic reticulum (ER) respectively, representing faults in collagen secretion (Zhao et al., 2016). Damage of function variations in *TMEM38B* produce functional to severe recessive OI (Rubinato et al., 2014; Lv et al., 2020). Similar to showed in mice, human fibroblasts from OI patients

with *TMEM38B* variations showed compact synthesis, discharge, and accumulation of type I collagen (Cabral et al., 2020).

Type XV OI (*WNT1*)

Type XV is an autosomal recessive inherited disorder has been selected based on the recognition of heterozygous variation in *WNT1* gene. It triggers on chromosome 12p13.12 comprising 04 exons (Fahiminiya et al., 2013; Keupp et al., 2013). The OI are recessively pattern of inheritance with severe forms of the disease, which are caused by change in genes that influence osteoblast differentiation comprising *SP7*, *WNT1*, and *CREB3L1* respectively. There are enormous progresses in understanding the genetic basis of OI, but unfortunately, this has not been attended by comparable advancement in terms of therapy. The children with type XV OI have recurrent fractures, dwarfism, bone abnormalities, blue sclera respectively, and cause death of early infant showed in table 1. It is documented that *WNT1* hypofunctional alleles effect in clinicals with lessen bone mass density in humans, platyspondyly and twisting of upper and lower limb bones (Keupp et al., 2013; Umair et al., 2017). Total 23 (11.38%) mutations were reported in 24 families, among these31 (6.93 %) male patients and 25 (6.42%) female patient was recorded from different ethnic origion (table 2&3). The *WNT1* gene protein plays vital role in the beta catenin system, which activates the bone synthesis (Beleggia et al., 2013; Line et al., 2013). In mice *Wnt1* is also termed as Swaying (Sw) mouse was first designated as bearing less developed coordination, with a turning movement design and cerebellar shortage. The Sw mouse was late created to be character like same to mice with a targeted *WNT1* variation producing osteopenia and gentle bones and was later renowned to be formed by a frame shift alteration in *WNT1* (Wnt1Sw), with homozygous (Wnt1Sw/Sw) mice stating the Sw features like common cracks, less bone mass and reduced bone strength correspondingly repeating the features of human patients (Joemg et al., 2014).

Type XVI OI (*CREB3L1*)

The *CREB3L1* gene present on chromosome 11p11.2 comprising 03 exons caused variation, as result Type XVI OI, is a recessive inheritance causing a severe demineralization, ossification of skull is reduced, blue sclera, multiple fractures in ribs and long bones extremities in the prenatal stage (Symoens et al., 2013). Total 04 (1.98%) mutations were reported in 4 families, among these 07 (1.56 %) male patients were recoded with no female ratio respectively (table 2&3). The patients have many clinical features such as demineralization, reduced ossification of skull, blue sclera, multiple fractures long bones, ribs, osteopenia and recurrent fractures showed in table 1. The OI are recessively pattern of inheritance with severe forms of the disease, which are caused

by change in genes that influence osteoblast differentiation comprising *SP7*, *WNT1*, and *CREB3L1* respectively. There are enormous progresses in understanding the genetic basis of OI, but unfortunately, this has not been attended by comparable advancement in terms of therapy (Ralston SH Gaston, 2020). The protein is usually translated by the gene, situated in the endoplasmic reticulum (ER) membrane. However, burden to the ER the present protein is cut and transmission to the cytoplasmic transcription factor domain translocate to the nucleus. It persuades the transcript of mark genes by attaching to box B elements (Mellor et al., 2013). To the CREB/ATF family, *CREB3L*1 is a basic leucine zipper (bZIP) transcription feature belonging. It is also called as old astrocyte specifically induced substance (OASIS), shares great physical similarities with ATF6. *CREB3L*1is extremely expressed in osteoblasts and homozygous removal in mice produces severe osteopenia because of reduced osteoblast role (Murakami et al., 2011). The genetic function of *CREB3L*1 identified in two parts like *CREB3L* directly fixes to a UPRE-like order in the Col1a1 promoter area to drive its appearance, and it also looks to control the discharge of matrix proteins (Murakami et al., 2009). Damage of function variations in *CREB3L*1 have been exposed to produce recessively inherited severe OI with regular fractures in human (Symoens et al., 2013).

Type XVII OI (*SPARC*)

OI, Type XVII is an autosomal recessive condition produced by alteration in *SPARC* gene sited on 5q31.1 chromosome comprising 10 exon respectively. The folks with type XVII have features like blue sclera, bowing of spine (scoliosis), hear impairment, dwarfism, joints difficulties (contractures), dentinogenesis imperfecta (DI) and respiratory problems showed in table 1 respectively (Mendoza-Londono et al., 2015). In 03 families, total 02 (0.99%) mutations were reported, among these 04 (1.02%) female patients and male ratio was 00% reported from different ethnic origion of the world (table 2&3). The *SPARC* lacking mice were produced by targeted disturbance. The mice seemed normal and fertile until 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 showed no qualitative variations in the main basal lamina proteins laminin, collagen IV and entactin (Bradshaw et al., 2003). In term of type XVII OI therapy, two types of bisphosphonates (BPs) are used. One type of non-nitrogen containing BPs that lead to apoptosis of osteoclasts by creating equivalents of ATP, while other type nitrogen-containing BPs have no influence. Without nitrogen containing BPs have higher efficacy for the hydroxyl apatite crystals (Nijhuis et al., 2019). Another remedy for the OI is Romosozumab, which enhance the

risk of myocardial infraction (MI), stroke, heart failure and death among patients with primary osteoporosis (Lv et al., 2020).

Type XVIII OI (*TENT5A*)

OI type XVIII is a recessive condition, caused by a homozygous change in the gene *TENT5A*, located on 6q14.1 chromosome comprising 03 exons. The *TENT5A* gene encodes the protein terminal transferase 5A protein, respectively. Common characteristic of type XVIII OI are characterized by congenital bending of long bones, blue sclera, wormian bones, vertebral failure, multiple fractures in the first years of life showed in table 1. OI type XVIII was informed in Italian boy causes one base pair duplication in *TENT5A* gene, producing frame shift forecast to result in an early termination codon. Similarly, in 04 children belonging 03 different consanguineous families with type XVIII OI reported mutation performed by the exome sequencing (Doyard et al., 2018). By analyzing N-ethyl N-nitrosourea, consequent mouse variants for high plasma, alkaline phosphatase action, tracked by exome sequencing, recognized a 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, like 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 (Diener et al., 2016).

Type XIX OI (*MBTPS2*)

The X link recessive gene *MBTPS2* is found on chromosome Xp22.12 containing 07 exons was known in type XIX OI. Homozygous or compound heterozygous mutation in *MBTPS2* gene categorized by prenatal fractures and generalized osteopenia, dwarfism, scoliosis, skeleton deformity and marked anterior angulation of the tibia showed in table 1. Membrane-bound transcription factor protease, site 2 (*MBTPS2*) is located in the Golgi apparatus membrane where it cuts substrates intricate in the ER stress response, comprising *CREB3L1*/OASIS, ATF6 and sterol regulatory element binding protein (SREBP). In 03 families, total 03 (1.48%) mutations were reported, among these 21 (4.69%) male patients and female ratio was 00% reported from different area of the world (table 2&3). A novel missense variant in *MPTBS2,* which affected an idea that is significant for protease catalytic purpose, produced moderate or severe X linked recessive form of OI in two autonomous families. In the similar study, OI patient osteoblasts displayed

compact cleavage of *CREB3L1*/OASIS and reduced LH1 levels related with reduced levels of hydroxylation of helical lysine (K87) and raised LP/HP ratio (Lindert et al., 2016).

Type XX OI (*MESD*)

OI type XX is an autosomal inheritance, caused by homozygous mutation in *MESD* gene located on chromosome 15p25.1 containing 03 exon. The individuals with type XX OI have blue sclera, dwarfism, and joint contractures; hear loss and scoliosis showed in table 1. Moreover, the patients have progressive irregularities of bone complication characterized by osteopenia and few patients have died from the lung failure (Moosa et al., 2019). Total 04 (1.98%) mutations were reported in 4 families, among these 4 (0.89%) male patients and 01 (0.25%) female patient was recorded from different ethnic origion (table 2&3). *MESD* gene translates an ER chaperone protein for the renowned wingless associated integration site signifying receptors *LRP5* and *LRP6*. Because full lack of *MESD* gene produces embryonic lethality in mice, we supposed that the OI related changes are hypomorphic alleles since these changes happen downstream of the chaperone action domain but upstream of ER maintenance domain (Moosa et al., 2019). The gene recognized in the mesoderm development (*MESD*) removal break on mouse chromosome 7, is important for requirement of embryonic polarization and mesoderm initiation. They recognized that the showing and cell difference faults identified in *MESD* removal homozygotes lead to only harm of the Mesdc2 gene and it is renamed as *MESD* gene (Hsieh et al., 2003). The researcher explained the boca an evolutionarily conserved gene in Drosophila melanogaster (fruit fly) that translates an ER protein homologous to the mouse Mesdc2 protein. They show that boca is particularly important for the intracellular functioning of partners of the LDLR family. Two LDLRs in flies, which are vital for wingless sign transduction, and yolkless, which is required for yolk protein approval during oogenesis, were observed to involve boca work (Culi et al., 2003).

Type XXI OI (*KDELR2*)

Recessive autosomal inheritance of type XXI is based on chromosome 7p22.1, which has five exons and encodes the protein that retains receptor 2 in the endoplasmic reticulum (ER) lumen. In both yeast and mammalian cells, resident soluble proteins that are continuously retrieved from a pre-Golgi compartment known as the cis-Golgi occupy the lumen of the ER. The following progressive anomalies are seen in patients with type XXI OI: wormian bones, blue sclera, DI, thin ribs, pectus excavatum, reduced bone mineral density, scoliosis, coxa-vera, bowing of the long bones, muscular hypotonia, and neurological issues, as listed in table 1. Total 06 (2.97%) mutations were reported, among these 07 (1.56%) male patients and 03 (0.77%) female patients were recorded from different ethnic origion (table 2&3). Two affected children, a girl and a boy, were

born to Pakistani parents who were consanguineous (first cousins). The *KDELR2* c.13C > T (p.Arg5Trp) and c.485 A > G (p.Tyr162Cys) missense mutations were discovered to be homozygous in both patients, who had significant motor delays and were unable to walk independently at 6 years and 2 years and 8 months of age (Efthymiou et al., 2021). *KDELR2*'s function in human development is not well understood. Nonetheless, research on *KDELR2* loss of function (LoF) in animals shows that it is crucial for embryonic development. The International Mouse Phenotypic Consortium (IMPC) characterized *KDELR2* LoF mice (Dickinson et al., 2016).

Type XXII OI (*CCDC134*)

Recessive autosomal inheritance of type XXII OI is found on chromosome 22q31.2, which only has 07 exons. The type XXII displayed the intrauterine fractures, scoliosis, kyphosis, shot stature, blue sclera, pectus excavatum, extreme bone fragility, repeated fractures, wormian bones, and bowing of long bones listed in table 1. The homozygous mutation (c.2T>C) in the *CCDC134* gene was found in two affected individuals who were Moroccan in origin (Dubail, et al., 2020). Total 01 (0.49%) mutations were reported, among these 01 (0.22%) male patients and 01 (0.25%) female patients were recorded from different ethnic origion (table 2&3). Huang used a lung cDNA library to clone human *CCDC134*. The determined 229-amino acid protein has an estimated molecular mass of 26.4 kD and includes a potential N-terminal signal peptide. With Northern blot analysis; it was possible to determine that the testis expressed a transcript measuring 1.3 kb, called *CCDC134*, at a higher level than the placenta or lung. *CCDC134* expression was detected by RT-PCR in a range of tumor tissues and cell lines, as well as in the adult human spleen, placenta, ovary, lung, and leukocytes. Endogenous *CCDC134* was synthesized as a 26-kD protein, altered by glycosylation to a 36-kD form, and ultimately existed as a 34-kD form after the signal peptide was removed, according to Western blot examination of multiple human cell lines (Huang et al., 2008).

Type XXIII OI (*PHLDB1*)

OI type XIII is an autosomal recessive inheritance caused by a mutation in the *PHLDB1* gene, which is present on chromosome 11q23.3 with 23 exons. Dwarfism, truncal obesity, blue sclera, osteopenia, bone fragility and fractures, platyspondyly, lumber lordosis, coxa-vera, bending of limbs, broadening of the wrist, and neurological abnormalities are among the conditions listed in table 1 for the children with type XXIII. Total 02 (0.99%) mutations were reported, among these 03 (0.67%) male patients and 02 (0.51%) female patients were recorded from different ethnic origion (table 2&3). After screening two afflicted individuals from Turkey, heterozygous mutations c.2392dup and c.2690_2693del reported. The pleckstrin homology-like domain family B member-1

(*PHLDB1*) protein, which is encode by *PHLDB1*, is involved in phosphorylation that is reliant on insulin. Tuysuz et al., 2023) observed a decline in *PHLDB1* expression levels in the skin fibroblast and blood samples when compared to the controls.

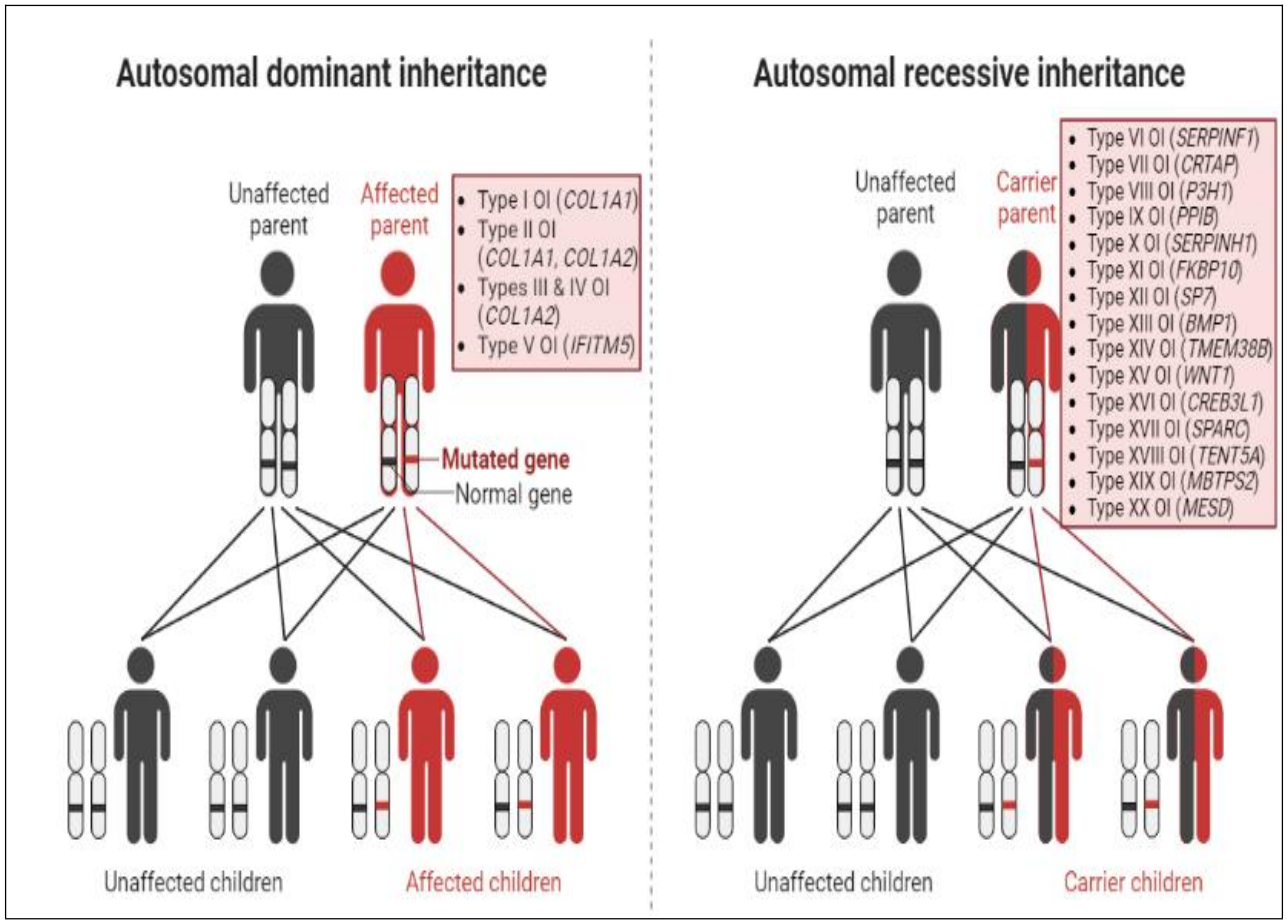

Table 2: *Number of reported mutations in genes causing human OI phenotypes*

			Type of Mutations			
Genes	OMIM	Reported Mutations	Missense /Non sense	Splice	Deletion /Insertion	References
COLIA1	120150	55 (27.22%)	22	18	15	Andersson et al., 2020
COLIA2	120160	23 (11.38%)	18	04	01	Andersson et al., 2020 Essawi et al., 2018

IFITM5	614757	02 (0.99%)	02	-	-	Farber et al., 2014
SERPINF1	172860	20 (9.90%)	10	02	08	Wang et al., 2017; Minillo et al., 2014
CRTAP	605497	14 (6.93%)	04	08	02	Cabral et al., 2007; Ben-Amor et al., 2014; Baldridge et al., 2015; Barbirato et al., 2015; Costantini et al., 2017
P3H1	610339	02 (0.99%)	02	-	-	Essawi et al., 2018
PP1B	123841	03 (1.48%)	02	-	01	Stephen et a., 2015; van Dijk et al., 2018,
SERPINH1	600943	02 (0.99%)	01	-	01	Essawi et al., 2018
FKBP10	607063	17 (8.41%)	08	-	09	Zhang et al., 2018; Umair et al., 2016; Kelley et al., 2016; Setijowati et al., 2012; Shaheen et al., 2011; Essawi et al., 2020; Schwarze et al., 2024; Li et al., 2019.
SP7	606633	01 (0.49%)	01	-	-	Hayat et al., 2020
BMP1	112264	08 (3.96%)	06	01	01	Valencia et al., 2014
TMEM38B	611236	03 (1.48%)	01	-	02	Essawi et al., 2018
WNT1	164820	23 (11.38%)	17	02	04	Sangsin et al., 2018; Xu et al., 2018; Volodarsky et al., 2018; Kuptanon et al., 2018; Pyott et al., 2013; Kausar et al.,

						2018; Liu et al., 2016
CREB3L1	616215	04 (1.98%)	02	-	02	Andersson et al., 2020
SPARC	182120	02 (0.99%)	02	-	-	Hayat et al., 2020
MBTPS2	300294	03 (1.48%)	03	-	-	Shaheen et al., 2011
MESD	607783	04 (1.98%)	01	-	03	Setijowati et al., 2012
KDELR2	619131	06 (2.97%)	02	-	-	Efthymiou et al., 2021, Dijik et al., 2020
CCDC134	619795	01 (0.49%)	01	-	-	Dubail et al., 2020
PHLDB1	620639	02 (0.99%)	-	-	02	Tuysuz et al., 2023
PLOD2	609220	05 (2.47%)	03	02	-	Puig-Hervas et al., 2012
Total	--	202 (100%)	108	37	51	---

Table 3: Gender wise of patients with different genes causing OI phenotypes.

Genes	Families members	Males	Females	Ethnic Origins	References
COLIA1	61	78 (17.44%)	61 (15.68%)	Sw, Ch, Pa,	Andersson et al., 2020; Zhang et al., 2016
COLIA2	25	48 (10.73%)	81 (20.82%)	Sw, Ch, Pa,	Essawi et al., 2018
IFITM5	32	25 (5.59%)	26 (6.68%)	Ca, Us, Uk, Vi, Af, Ko, Au, Ge,	Farber et al., 2014; Guillemyn et al., 2019; Alhamdi et al., 2018
SERPINF1	20	30 (6.71%)	13 (3.34%)	Pak, Ar, Ca, It, Pa, Ch, Br, Tu, In,	Becker et al., 2011; Keller et al., 2018; Cayami et al., 2019
CRTAP	16	36 (8.05%)	22 (5.65%)	Ar, Pa, Su, Cau, Br, Fi, In,	Barbirato et al., 2015; Costantini et al., 2017
P3H1	02	08 (1.78%)	55 (14.13%)	Palestine	Essawi et al., 2018; Guillemyn et al.,

					2019
PP1B	03	01 (0.22%)	05 (1.28%)	North Eur, Pak, In,	Stephen et al., 2015; van Dijk et al., 2009
SERPINH1	02	03 (0.67%)	00 (00.00%)	Palestine, Ar,	Essawi et al., 2018
FKBP10	40	37 (8.27%)	56 (14.39%)	Pak, Tu, In, So Af, Cau, Pa, Ind, Ch, Us, Ar,	Kelley et al., 2016; Li et al., 2019
SP7	01	01 (0.22%)	00 (00.00%)	Pakistan	Hayat et al., 2020
BMP1	07	72 (16.10%)	11 (2.82%)	Pak, Thai, Ch, Pa, Egy,	Lu et al., 2018; Xu, et al., 2018
TMEM38B	16	28 (6.26%)	22 (5.65%)	Arab, Israel, Palestine	Volodarsky et al., 2013; Essawi et al., 2018
WNT1	24	31 (6.93%)	25 (6.42%)	Pak, Tu, Egy, Thai, Ch, Neth, In, Us,	Kausar et al., 2018; Liu et al., 2016
CREB3L1	04	07 (1.56%)	00 (00.00%)	Tu, Ind, Sw, Us,	Lu et al., 2018; Laine et al., 2013
SPARC	03	00 (00.00%)	04 (1.02%)	Pakistan, Canada,	Hayat et al., 2020
MBTPS2	03	21 (4.69%)	00 (00.00%)	Thailand, Germany	Lindert et al., 2016
MESD	04	04 (0.89%)	01 (0.25%)	Br, Tu, Pur,	Moosa et al., 2019
KDELR2	10	07 (1.56%)	03 (0.77%)	Pakistan, Du, Sp	Efthymiou et al., 2021, Dijik et al., 2020
CCDC134	02	01 (0.22%)	01 (0.25%)	Morocco	Dubail et al., 2020
PHLDB1	05	03 (0.67%)	02 (0.51%)	Turkey	Tuysuz et al., 2023
PLOD2	07	06 (1.34%)	01 (0.25%)	Egy	Puig-Hervas et al., 2012
Total	287	447 (100%)	389 (100%)	------	------

Sw=Sweden, Ch=China, Pa=Palestine, Ca=Canada, Us=USA, Uk=Ukraine, Vi=Vietnam, Af=Africa, Ko=Korea, Au=Australia, Ge=Germany, Pak=Pakistan, Ar= Arabia, It=Italy, Br=Brazil, Tu=Turkey, In=India, Su=Sudan, Cau=Caucasian, Fi=Finland, North Eur=Northern Europe, So Af=South Africa, Indonesia, Thai=Thailand, Egy=Egypt,

Is=Israel, Pur= Portugal, Neth=Netherland, Du=Dutch, Sp=Spanish.

Conclusion and Perspective

OI is a heterogeneous group of clinical and genetic variation. Among this variation, cluster of genes involved, alteration in these genes formed truncated type I collagen leading to impair growth synthesis with decrease bone mass density and enhance the risk of fractures. The genetics of OI is a highly complicated and did not concern only to the Mendelian inheritance. Numerous other features comprising variable expressivity, imperfect penetrance, difference in molecular background, and molecular and allelic heterogeneity, epigenetic features, and related genes, diverse type of environmental and developmental affect are possibly played very important roles in emerging different clinical features in human.

Moreover, several genetic detailed, epidemiological and embryological studies had shown a substantial differences in the clinical, incidence, expressivity and signifying a high etiological of phenotypic heterogeneity. In previous various researchers have attempted to create a classification system for OI. Different OI classifications, their benefits and back draws has been obtainable in Table 1. Through the beginning of new techniques like RNA sequencing, bioinformatics tools, next-generation sequencing (NGS) and pathogenic mutations will established that lead to creating the genotype–phenotype relationships in the future. RNA sequencing can investigate the constantly altering transcriptome, post-transcriptional modifications, alternate spliced transcripts, single nucleotide polymorphisms (SNPs) disease causing mutations, gene union and expression over time. In the current years, whole genome sequencing (WGS), whole exome sequencing (WES), (NGS) has enormously enhanced the screening of families and sporadic cases providing rapid, precise and in low price genetic analysis. Appropriate genotype-phenotype relationships can helpful in genetic screening, control medical disorders, improve our knowledge regarding newest diagnosed diseases and their related genes mutations identified by NGS tools in future. Moreover, the influences of pathogenic mutations in causal gene can cause the concerned clinical features, while various mutations can clarify the phenotypic variability in numerous cases. Large sequencing data with correct clinical information's can lead to improve the predictive clinical models providing the newest grouped regulatory interspaced small palindromic repeats/CRISPR connected protein 9 (CRISPR– Cas9) skills might helpful to understand the bones developmental mechanisms and also explain the pathogenesis of OI and transmit on investigational treatment study. These policies can diagnose maximum yield genetic goals for therapeutic interventions, which still stay a challenge for future research study.

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