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Osteogenesis Imperfecta: An Update

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Abstract

Osteogenesis imperfecta (OI) is a rare, heritable systemic disorder of bone and connective tissue that has varying phenotypic heterogeneity -varying degree of bone fragility, blue sclerae, dentinogenesis imperfecta, short stature, scoliosis, and joint hyperextensibility. For decades only autosomal dominant forms caused by *COL1A1* and *COL1A2* genes were recognized. But since past decade with advancement in molecular technologies new genes have been identified leading to recognition of autosomal recessive OI. Currently there are around 17 genes for OI. The classification of OI thus is now based on genetic analysis. In the following review we aim to discuss the different types of OI, classification based on molecular basis, different genes causative of OI and their pathophysiology and mechanisms. An approach to a suspected case of OI, differentials and the most recent management and therapeutic options for OI are discussed.

Introduction

Osteogenesis Imperfecta (OI) or "brittle bone disease" is a rare phenotypically and genetically heterogeneous group of heritable connective tissue disorders characterized by easy fracturing of bones, with or without bony deformities, blue sclera, joint laxity and dentin defect. It shows wide range of clinical presentation varying from a lethal perinatal form to a mild disorder (Figure 1). Very mild case may only become evident in adulthood, manifesting as premature osteoporosis. The incidence of OI varies from approximately 1/15,000–20,000 (Marini et al., 1988) though no data is available from India.

The earliest known patient with OI dates from about 1000 BC and appears to be an Egyptian infant, evidence of which can be drawn from studying the remains of Egyptian mummy. The classical classification by Sillence had four types depending on the clinical features and the severity. These groups can be distinguished as type I (mild OI, blue sclerae, autosomal dominant inheritance), type II (lethal perinatal OI, autosomal recessive inheritance, later subdivided in II-A, -B, and -C based on radiographic features, type III (progressively deforming autosomal recessive inheritance), and type IV (dominantly inherited OI with normal sclerae). Aglan et al., 2012 proposed the scoring system for the assessment of clinical severity including 5 major criteria, namely, average number of fractures per year, motor mile stones, long bones deformities, length/height standard deviation score and z-score of the mineral bone density.

Autosomal Dominant Osteogenesis Imperfecta

Most families of OI show a dominant pattern of inheritance. OI type I to OI type IV account for 90% of all OI cases. Chu et al. in 1983 first reported the presence of an internal deletion of about 0.5 kb in one allele for pro-α1 (I) chain (*COL1A1*) in a patient with OI. Since then about 1500 mutations in these genes have been known. Ninety percent of the cases are caused by heterozygous mutations in *COL1A1* or *COL1A2* genes. There is no genotype – phenotype correlation and mutations in either *COL1A1* or *COL1A2* can cause any of the four types of OI. In spite of identifying these causative genes in 1980s; the etiology of remaining 10% cases continued to remain unknown for long. Recurrences in the families with severe types OI like type II or III were attributed to germ line mosaicism. One more gene for autosomal dominant varieties of OI other than *COL1A1* and *COL1A2* is *IFTM5* for OI V (Cho et al., 2012). OI type V has distinguishable radiographic features of hypertrophic callus formation and ossification of introsseus membr-

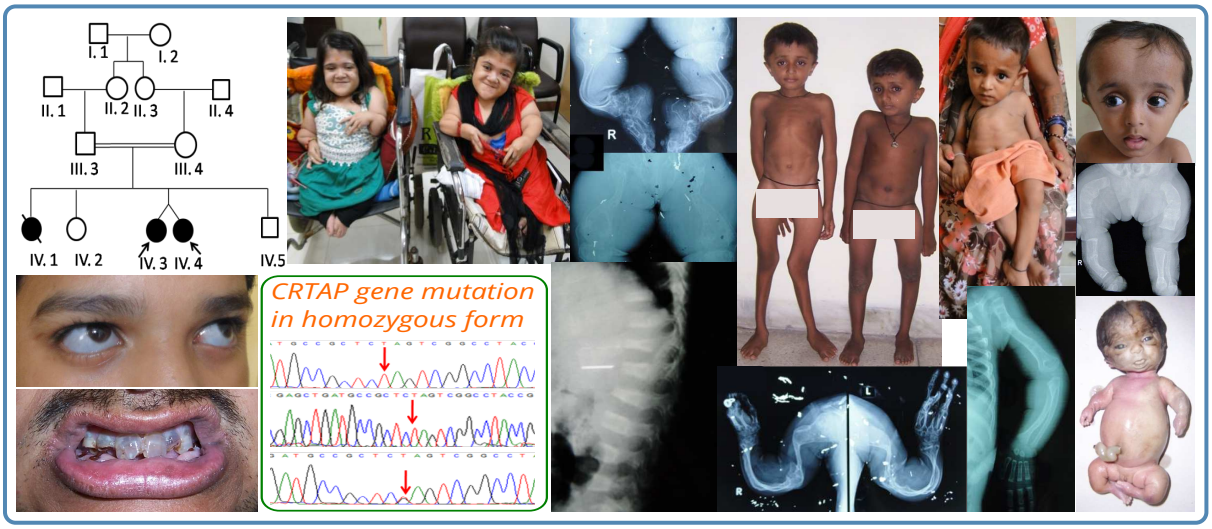

Figure 1 Patients with Osteogenesis Imperfecta, showing clinical variability, characteristic clinical and radiological features.

ane of forarm bones. In one report from India, It has been observed that bisphosphonates may exacerbate callus hyperplasia, and may therefore have to be used with caution in patients with type V osteogenesis imperfect (Ranganath et al., 2016). There are other phenotypes also which are caused by *COL1A1* and *COL1A2* mutations namely; caffey disease (infantile cortical hyperostosis), classic Ehlers-Danlos syndrome, EDS arthrochalasia type, and osteoporosis.

Autosomal Recessive Osteogenesis Imperfecta

Recent developments have generated a new paradigm for OI and it has been found that a proportion of cases of OI are caused by the defects in the genes which are involved in regulation of the synthesis of type I collagen pro alpha polypeptide chains, proteins involved in type I collagen processing in the endoplasmic reticulum and proteins involved in osteoblast function. These cases of OI are inherited in autosomal recessive fashion. The first gene for autosomal recessive OI was identified in 2006 (Morello et al., 2006). This was *CRTAP* gene encoding cartilage-associated protein (*CRTAP*) and was found to be the cause of OI type VII. Presently, thirteen genes of recessive OI have been identified (Table 1). *CREB3L1* gene causes autosomal recessive form (OI XVI) and this is due to the contiguous gene deletion on chromosome 11p11 encompassing *CREB3L1*) (Symoens et al., 2013). Bruck syndrome is a syndromic form of OI associated with joint contractures caused by homozygous mutation in *PLOD2* gene.

In addition two genes on X chromosome are identified as etiologies of OI; increasing the number of genes for OI to 18. Loss-of-function mutations in *PLS3* encoding plastin-3 were discovered as a cause of one form of X-linked osteoporosis with fractures (van Dijk et al., 2013). Recently, Lindert et al., 2016 identified an X-linked form of osteogenesis imperfecta in two independent pedigrees. Phenotypic inheritance pattern, linkage analysis and next generation sequencing (NGS) were used to localize the causative gene in each family to *MBTPS2* at Xp22.

The first 4 subtypes of OI (clinical phenotypes) are caused by *COL1A1* and *COL1A2* genes. Further numbering upto XVII types (showing clinical overlap with initial four subtypes) is included in OMIM based on the causative genes and all of them are autosomal recessive inheritance except OI V. Data from India shows that *COL1A1* and *COL1A2* mutations contribute to only 70% of cases with OI (Stephen et al., 2014). High level of consanguinity is probably the main contribute to the higher prevalence of autosomal recessive OI. A small number of cases with recessive OI are reported from India (Stephen et al., 2015). The products of the genes for recessive types of OI are mostly enzymes which involves in the post translational modification of the pre pro type I collagen produced from *COL1A1* and *COL1A2* genes. The functions of these genes include lysyl 3 hydroxylation, collagen processing and maturation, collagen stability and bone formation and homeostasis. More genes are still getting

identified. These disorders being very rare most of the publications report only a few cases. There is no large scale case series involving study of multiple genes.

As can be seen in table 1, the functions of the genes causing OI are collagen synthesis, modification, folding and crosslinking. In addition to mutations in *COL1A1* and *COL1A2* genes, defects in osteoblast development like *CREB3L1* and *WNT1* also cause OI. *CRTAP*, *LEPRE1* and *PPIB* are important proteins of the complex involved in hydroxylation of propyl 3 complex which plays a critical role for the proper collagen helix formation in the cell. Improved understanding of functional pathways of collagen is paving ways to different treatment strategies.

Table 1 Classification of classic dominant and new recessive forms of Osteogenesis Imperfecta.

OI Type	Defective Gene (Reference)	MIM No.	Protein Name	Protein function	Clinical phenotype
Autosomal Dominant inheritance					
I	*COL1A1* (Mottes et al., 1990)	120150	Collagen type I alpha chain	Formation of triple helix of type I collagen	Alter the structure or quantity of type I collagen and cause a skeletal phenotype ranging from subclinical to lethal
II	*COL1A1* or *COL1A2* (Mottes et al., 1990)	120150 120160	Collagen type I and type II alpha chain respectively		
III	*COL1A1* or *COL1A2* (Mottes et al., 1990)	120150 120160	Collagen type I and type II alpha chain respectively		
IV	*COL1A1* or *COL1A2* (Mottes et al., 1990)	120150 120160	Collagen type I and type II alpha chain respectively		
V	*IFITM5* (Cho et al., 2012)	614757	Bone-restricted Ifitm-like (BRIL)	Osteoblast formation in early mineralization stage	Characterized by calcification of the forearm interosseous membrane, radial head dislocation and hyperplastic callus formation
Autosomal recessive inheritance					
VI	*SERPINF1* (Becker et al., 2011)	172860	Pigment-epithelium derived factor (PEDF)	Inhibits osteoclast maturation by stimulating osteoprotegerin (OPG) expression	Characterized by reduced bone mineralisation
VII	*CRTAP* (Morello et al., 2006)	605497	Cartilage-associated protein (CRTAP)	Components of the collagen prolyl 3-hydroxylation complex which plays a critical role for the proper collagen helix formation in the cell	Severe to lethal bone dysplasia with rhizomelia
VIII	*LEPRE1* (Cabral et al., 2007)	610339	Prolyl-3-hydroxylase 1 (P3H1)		
IX	*PPIB* (van Dijk et al., 2009)	123841	Cyclophilin B (CypB)	Isomerisation of peptidylprolyl bonds, crucial for proper collagen folding	Severe to lethal bone dysplasia with rhizomelia

X	*SERPINH1* (Christiansen et al., 2010)	600943	Heat-shock protein 47 (HSP47)	Recognize and help maintain the folded state of type I procollagen trimer	Results in moderately severe form of OI, characterized by osteopenia, bone fragility and skeletal deformities
XI	*FKBP10* (Alanay et al., 2010)	607063	FK506 binding protein, 65kDa (FKBP65)	Effects on procollagen through collagen modifying enzymes	Results in moderately severe form of OI, characterized by osteopenia, bone fragility and skeletal deformities
XII	*SP7* (Lapunzina et al., 2010)	606633	Osterix, transcription factor Sp7 (SP7)	Important role in bone formation	Characterized by recurrent fractures, mild bone deformations, generalized osteoporosis and delayed teeth eruption
XIII	*BMP1* (Asharani et al., 2012)	112264	Bone morphogenetic protein 1 (BMP1)	Functions as the procollagencarboxy-(C)-proteinase for types I to III procollagen; Play key role in ECM assembly and tissue patterning	Characterized by normal teeth, faint blue sclera, sever growth deficiency, borderline osteoporosis
XIV	*TMEM38B* (Volodarsky et al., 2013)	611236	Transmembrane protein 38B (TMEM38B)	Functions as a monovalent cation channel; affect Ca2+ homeostasis in the ER	Characterized by variable degrees of severity of multiple fractures and osteopenia, with normal teeth, sclera and hearing
XV	*WNT1* (Keupp et al., 2013)	164820	WNT1	Activates expression of several genes implicated in bone formation	Characterized by early-onset recurrent, bone deformity, significant reduction of bone density, short stature
XVI	*CREB3L1* [contiguous gene deletion on chromosome 11p11 encompassing *CREB3L1*] (Symoens et al., 2013)	616215	Old astrocyte specifically induced substance (OASIS)	An endoplasmic reticulum-stress transducer that alters the transcription of target genes involved in developmental process, differentiation or maturation upon mild ER-stress	Characterized by osteopenia and spontaneous fractures
XVII	*SPARC* (Mendoza-Londono et al. 2015)	182120	Secreted protein, acidic, cysteine-rich (SPARC)	Expressed by osteoblasts; binds to collagen type I and other matrix proteins	Progressive osteoporosis due to defect in bone formation

Bruck Syndrome (syndromic OI)	*PLOD2* (Puig-Hervas et al., 2012)	601865	Lysyl hydroxylase (LH2)	It encodes lysyl hydroxylase 2 which also has a role in the hydroxylation of collagen telopeptide lysine	Characterized by congenital contractures of the large joints
X-linked inheritance					
X-linked recessive OI	*MBTPS2* (Lindert et al., 2016)	300294	Site-2 metalloprotease (S2P)	Sterol control of transcription and endoplasmic reticulum (ER) stress response	Characterized by bowing of upper and lower extremities, prenatal fractures and scoliosis
X-linked osteoporosis	*PLS3* (van Dijk et al., 2013)	300131	Plastin-3	PLS3 is an actin-binding/bundling protein	Characterized by decreased bone mineral density (BMD)

Approach to a Case of OI

Clinical diagnosis of a most of the cases is relatively easy and straightforward. Radiological evidence of decreased bone density along with history of repeated fractures and / or fractures with trivial trauma suggests the diagnosis. Presence or absence of blue sclera, dentiginous imperfecta, large open fontanelles, wormian bones and pre-senile deafness helps in the diagnosis and clinical classification. Other causes of decreased bone density need to be ruled out by associated findings and investigations (Table 2).

Differential diagnoses for antenatal cases: In utero, short and undermineralised bones, fractures can be appreciated in utero and lead to suspicion of OI. The following conditions need to be ruled alongwith–

• Hypophasphatasia - characterized by defective mineralization of bone and/or teeth in the presence of low activity of serum and bone alkaline phosphatase. Clinical features range from stillbirth without mineralized bone at the severe end to pathologic fractures of the lower extremities in later adulthood at the mild end.

• Thanatophoric dysplasia- neonatal lethal short-limbed dwarfing condition, well-ossified spine and skull, platyspondyly, ventriculomegaly, narrow chest cavity with short ribs, polyhydramnios, and bowed femurs (TD type I), cloverleaf skull (kleeblattschaedel) (often in TD type II; occasionally in TD type I) and/or relative macrocephaly.

• Campomelic dysplasia- skeletal dysplasia characterized by distinctive facies, Pierre Robin sequence with cleft palate, shortening and bowing of long bones, and club feet. Other findings include laryngotracheomalacia with respiratory compromise and ambiguous genitalia or normal female external genitalia in most individuals with a 46,XY karyotype.

• Achondrogenesis - extremely short limbs with short fingers and toes, hypoplasia of the thorax, protuberant abdomen, and hydropic fetal appearance caused by the abundance of soft tissue relative to the short skeleton.

Family history is important in the evaluation of a case with suspected OI, as milder/mosaic/asymptomatic forms are difficult to detect clinically. A three generation pedigree should be drawn and the family should be asked for history of recurrent easy fractures, short stature, presenile deafness in any of the family members. Presence of consanguinity suggests the possibility of an autosomal recessive disorder. In some cases the definitive diagnosis of OI may be difficult and confirmation by mutation testing is essential.

Molecular Diagnosis

Mutation detection confirms the diagnosis and is essential for genetic counseling regarding risk of recurrence and preventing recurrence by way of prenatal diagnosis. The heterogenic etiology and large sizes of genes makes mutation detection a complex process. The causative gene mostly cannot be predicted based on the clinical features as there is no genotype phenotype correlation. Presence of hypertrophic callus and ossification of interosseous membrane is characteristic of OI type V for which only one causative mutation (c.-14C>T in *IFITM5* gene) is reported in all the cases. The severity of the presentation also does not provide

Table 2 Differential diagnosis postnatal.

Disorder	Clinical Features	Investigations	Comments
Pseudoglioma -Osteoporosis syndrome (OMIM 259770)	Bone fragility and fractures, Narrow diaphysis, hypotonia and eye abnormalities that lead to vision loss	Ophthalmological evaluation	Intelligence is usually normal
Hypophoshatasia	Wide sutures, poorly formed teeth, metaphyseal cupping, poorly formed teeth, bony spurs	Decreased serum alkaline phosphatase, hypercalcemia, hypercalciuria	Perinatal, infantile, childhood and adult forms are known
Disorders of osteolysis- Hajdu Cheney Syndrome, etc.	Joint contractures, pain in joints, gingival hyperplasia	Osteolysis of carpal and tarsals, acro-osteolysis	May have renal dysfunction
Thalassemia & other chronic hemolytic anemias	Hepatosplenomegal, hemolytic facies	Anemia, high level of fetal hemoglobin or presence of abnormal hemoglobin	Non-transfusion dependent thalassemia may present with fractures on trivial trauma and decreased bone density
Battered child	Disturbed family situation, marks of injury	Ruling out other causes is necessary. Normal BMD.	High level of suspicion is necessary

any clue the causative gene. Initially when *COL1A1* and *COL1A2* were the only known genes, collagen analysis was done to decide the possible causative gene. Later, DHPLC (Denaturing High Performance Liquid Chromatography) was used as a screening technique to identify the location of mutation and then the specific exons were sequenced. Such type of screening was essential as both the genes are large genes with 51 and 52 exons in *COL1A1* and *COL1A2* respectively. Identification of newer genes for OI has increased the complexities of molecular diagnosis. Next Generation Sequencing (NGS) is of great help in this disorder associated with a large number of genes, some of which have a large number of exons. A panel of all OI genes or sequencing of all genes of clinical relevance (Exome sequencing) is the test of choice. The studies on the detection rates and relative contribution of various genes to OI are still not available. Published data about mutations in genes other than *COL1A1* and *COL1A2* is limited worldwide and hence, more information about phenotypes of recessive OI is needed.

Management

The basic serum chemistries- serum calcium, phosphate, vitamin D and alkaline phosphatase are normal in patients with OI. However these values might be slightly elevated after a fracture. But as the patients started on bisphonates, grow older, have sedentary lifestyle due to bony deformities and fractures, the calcium and vitamin D levels fall. This can lead to delayed healing of fractures and increased bone fragility. So, it is recommended to supplement calcium and vitamin D in patients with OI according to the age group. There is still no "optimal treatment" for OI, both for limiting or preventing fractures and pain relief and improved mobility. Also, critical assessment of treatment outcomes is limited by the small numbers of participants in clinical trials and the short duration of many trials, which is frequently limited to 1 or 2 years of observation. The following table provides the list of various treatment modalities (Table 3).

Table 3 Various treatment strategies.

Existing treatment strategies: 1. Bisphosphonates 2. Teriparatide 3. Denosumab
New therapeutic approaches: 1. Antisclerostin antibody 2. Cathepsin K antibody 3. Transforming growth factor-β 4. Prenatal and postnatal transplantation of mesenchymal stem cells
Multidisciplinary management 1. Orthopaedic treatment 2. Rehabilitation

- Existing treatment strategies:

1. Bisphosphonates- Bisphosphonates, oral and intravenous decrease osteoclastic bone resoprtion. Various studies have shown variable efficacy of bisphosphonates on decreasing the fracture frequency and symptomatic relief of pain. The variability of response may be due to differential effects of bisphosphonates on various types of OI; the issue which may be solved with studies on mutation proved cases of OI. For example, we found that bisphosphonates increased callus formation in a case with type V OI (Dwan et al., 2014).

The findings of the 2014 Cochrane review (Dwan et al., 2014) for oral and intravenous Bisphosphnates in OI can be summed up as follows-

a. The oral or intravenous bisphosphonates increase bone mineral density in children and adults with OI, the effect not being different with the different bisphosphonates.

b. It is unclear whether oral or intravenous bisphosphonate treatment consistently decreases fractures, though there is no increased fracture rate.

c. The studies included in the Cochrane review do not show bisphosphonates conclusively improve clinical status (reduce pain; improve growth and functional mobility) in people with OI.

2. Teriparatide- Teriparatide is human recombinant parathyroid hormone, which increases bone mass by increasing osteoblast bone formation. It is highly effective in the treatment of age-related osteoporosis.

The few randomized trials of teriparatide in OI patients show increased BMD, especially in Type 1 OI than in individuals with OI types IV and III, but there was no significant decrease in number of fractures (Orwoll et al., 2014).

3. Denosumab (anti-RANK-ligand antibody)- The RANK, RANKL complex regulates bone-remodeling cycles by regulating osteoblast/osteoclast coupling and osteoclast differentiation. RANK is present on the osteoclast precursor, and RANKL produced by the osteoblast is part of the TNF superfamily and, along with the soluble decoy receptor osteoprotegerin, are essential regulators of osteoclast development and function. Denosumab is a human monoclonal antibody to RANKL; studies involving age-related osteoporosis have showed the efficacy of denosumab in reducing signaling via RANK, leading clinically to prevention of bone loss (Hoyer-Kuhn et al., 2014).

Due to poor response to Bisphsphonates in OI Type VI, Denosumab was tried with success in OI Type VI leading to BMD increase, normalization of vertebral shape, and decrease in fracture rate. Denosumab treatment also improved BMD and longitudinal bone growth in two children with *COL1A1/A2* mutations previously treated with Bisphosphonates.

- New therapeutic approaches:

1. Antisclerostin antibody - Sclerostin is a negative regulator of bone formation released from osteocytes that modulates osteoblast activity acting through Wnt/β-catenin pathway. Preclinical studies have demonstrated that treatment with antisclerostin monoclonal antibody acts as osteoanabolic therapy improves bone mass and bone strength, and enhances repair of fractures in animal models.

2. Cathepsin K antibody - Cathepsin K is highly expressed in osteoclasts and is an essential enzyme involved in the degradation of type I collagen in the organic bone matrix. In an animal model, the cathepsin K monoclonal antibody (Odanacatib) effectively suppressed bone resorption. A phase III randomized, placebo-controlled trial assessed the effect of Odanacatib on fracture risk over 5 years of treatment in women with osteoporosis, has shown increase in BMD and a significant reduction in the risk of fractures. Applicability to the collagen defect in OI remains to be determined.

3. Transforming growth factor-β - TGF-β is produced by osteoblasts and acts to coordinate bone remodelling by coupling osteoblasts and osteoclasts in the process of bone remodelling. TGF-β is secreted predominantly in an inactive latent form and is deposited into the bone ma-

trix. It has been reported that excessive TGF-β signaling is a mechanism of OI in both recessive and dominant OI mouse models. Also, treatment of mice with the anti-TGF-β neutralizing antibody 1D11 corrected the bone phenotype and improved lung abnormalities in both recessive and dominant forms of OI.

4. Prenatal and postnatal transplantation of mesenchymal stem cells - Severe to lethal forms of OI may be diagnosed in utero by ultrasonography starting at the 16th week. Following prenatal and postnatal cell transplantation in OI improvement was seen in linear growth and fractures were reduced in number, in fetus, neonatal and later life. In humans, improvement of linear growth and reduction of fracture rate followed prenatal and postnatal cell transplantation in OI. Additionally, prenatal transplantation of allogeneic MSCs in three OI pregnancies indicated that it has appeared to be safe. A clinical trial in human pregnancy is currently in progress. (Westgren et al., 2015).

- Multidisciplinary management: Orthopedic management might be necessary in cases of severe bone deformity impairing function, with recurrent fractures and nonunion of fractures. To date, there are no physiotherapeutic treatment protocols available for children and adults with OI. A recent study investigated a rehabilitation approach combining resistance training, body-weight-supported treadmill training, and neurodevelopmental treatment associated with side-alternating whole-body vibration in 53 individuals with OI (ages 2.5–24.8 years) for 6 months within a period of 12 months of treatment. There was improvement of mobility between, and also an increase in lean mass and BMD was observed (Hoyer-Kuhn et al., 2014). Further studies are needed to address the role of rehabilitation in OI patients.

Genetic Counseling and Prenatal Diagnosis

Bisphosphonates has given some relief to some patients of OI; though for many cases the life continues to be painful and handicapping. Molecular diagnosis can differentiate between OI inherited in dominant or recessive fashion and accurate risk of recurrence can be provided to the families. Mutation based prenatal diagnosis can be provided at early gestation and to all families. In situations without molecular diagnosis, ultrasonographic based diagnosis before 20 weeks of gestation for case with lethal variety of OI. For other varieties, shortening and bending of femora may be seen in some cases and may be in the later part of pregnancy. However, normal length and shape of long bones in a fetus cannot rule out OI.

Conclusion

Last decade has improved understanding of genetics of OI due to identification of many more genes for OI. NGS based diagnostics has provided simple strategy in clinical settings and is also identifying new genetic etiologies in research settings. Autosomal recessive OI is probably more common in India due to high prevalence of consanguinity and makes molecular diagnosis of each case essential as the risk of recurrence is 25% and phenotype is usually severe in recessive varieties of OI. New treatments may provide specific drug for specific type of OI and improve the outcome.

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