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The genetic landscape of osteogenesis imperfecta: mutational mechanisms and therapeutic targets

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Abstract

Osteogenesis imperfecta is colloquially known as brittle bone disease because it is an inherited disease characterized by a connective tissue disorder that causes decreased bone mass, increased bone fragility and abnormalities in skeletal structure.

This disease is caused by a mutation in the type I collagen genes, specifically COL1A1 and COL1A2, resulting in a variety of clinical manifestations ranging from mild to lethal.

The impact on the quality of life of patients with OI can be complicated, which is why they need multidisciplinary management strategies including orthopedic care, physical therapy, pain management and surgical interventions.

Keywords: Osteogenesis imperfecta; Mutation; Type I collagen; Brittle bone disease; Bone fragility

1. Introduction

Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous hereditary disease of connective tissue, with a wide spectrum of clinical expression, the main cause of which is a genetically determined violation of the quality of bone tissue, leading to frequent fractures with the development of disabling bone deformities and a complex of concomitant problems on the part of the respiratory, cardiovascular, neuromuscular systems, since type I collagen is a protein present in all supporting tissues (1).

The disorders comprising OI include anomalies in the structure or quantity of collagen, as well as post-transcriptional modifications involving folding, intracellular transport, or incorporation into the bone matrix (1,2).

The key feature that distinguishes OI from other early-on set bone fragility conditions is the hypermineralization of the bone material itself, so it is also known as “brittle bone disease”, although increased mineralization density is not the only contributor to brittleness. Mutations in the type I collagen synthesis and processing pathways, along with defects in accessory proteins such as PEDF (type VI OI) and those associated with reduced type I collagen production (type V OI) all share the bone material hypermineralization phenotype (3).

OI occurs with a prevalence of 1:10,000–1:20,000 and is considered a rare condition. OI arises due to both quantitative and qualitative defects in type 1 collagen, or through the interaction of proteins with this collagen (4).

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In addition, 90% of patients with OI have mutations in the *COL1A1* (OMIM: 120150) or *COL1A2* (OMIM 120160) gene, which encodes for alpha-1 and alpha-2 chains in type 1 collagen (5).

Previous studies categorize OI into four subtypes (types I–IV) based on clinical findings, inheritance patterns, and radiographic features: OI type I is the mildest form, OI type II is the perinatal lethal form, while OI type III is the most severe form, and OI type IV is characterized by the mild to moderate form. With an in-depth understanding of OI disease, more subtypes have been defined and added into OI's original classification system, making the number of subtypes updated to 18 (6).

OI is characterized by a wide range of clinical manifestations. Due to its variability in severity, it can be challenging to diagnose, especially in children. Susceptibility to fractures is a characteristic trait, however, these fractures can be attributed to normal childhood activities or even misinterpreted as signs of abuse.

Characteristic features such as short stature, skeletal deformities, and blue sclera can provide important clues to diagnosis, but they are not always present or recognized. In addition, genetic testing can confirm the diagnosis by identifying mutations in genes associated with OI, such as COL1A1 and COL1A2.

It is critical to raise awareness among healthcare professionals about the possibility of OI in cases of unexplained fractures, especially in infants and young children, to prevent misdiagnoses and ensure timely management and support for affected individuals and their families. Early detection can lead to better outcomes through the implementation of appropriate interventions and support services.

This article is a review of the genetic cause of OI as well as its different types and clinical manifestations in order to achieve an accurate diagnosis and to be able to apply the different treatments currently available.

2. Type I collagen

Type I collagen is a crucial structural component of the extracellular matrix present throughout the body. It plays a vital role in the formation of bones, ligaments, tendons, cartilage, skin, liver, heart valves, cornea, lungs, and other connective tissues. Its function is to provide support and resistance to tension to tissues. This protein is synthesized in the endoplasmic reticulum (7).

3. Synthesis of Type I Collagen

It is initially synthesized as a precursor form, procollagen, consisting of two identical pro-α1 and one pro-α2 chains, encoded by *COL1A1* and *COL1A2*, respectively, for the three chains to intertwine correctly, they must have a glycine residue at every third position. The N- and C- terminal propeptide of procollagen are cleavage by N-proteinase and C-proteinase correspondingly, to form the central triple helix structure with Gly-X-Y repeat units (2).

It is crucial to know the association between mutations in COL1A1 and COL1A2 genes as it is involved in the development of OI, as well as certain types of Ehlers-Danlos syndrome, Caffey diseases, and the overlapping diseases of OI /Ehlers-Danlos syndrome (2).

4. Molecular Changes in OI

Molecular changes in OI: Null alleles (absent or non-functional gene product) in the COL1A1 gene, resulting in reduced amounts of normal α1 chain, lead to a milder phenotype; missense mutations (point mutation resulting in altered amino acid sequence) in either COL1A1 or COL1A2 lead to more severe phenotypes, including lethal disease. Most mutations causing more severe OI result from the substitution of glycine by another amino acid that interrupts the tight coiling of the triple helix, delaying the process and allowing additional posttranslational modifications of the collagen molecules to occur, distorting their 3D structure (8).

The mineralization of the bone matrix is an essential process for the formation and maintenance of normal bone structure; collagen provides a scaffold for the deposition of minerals such as calcium and phosphorus. In contrast, alterations in bone mineralization are observed in OI. Specifically, mutations resulting in the substitution of glycine by another amino acid in the alpha chains of collagen can disrupt the tight winding of the collagen triple helix, delaying the mineralization process and allowing the appearance of additional post-translational modifications in collagen

molecules. As a result, the three-dimensional structure of collagen is distorted, and bone mineralization is compromised (8).

In some subtypes of OI, such as types V and VI, specific defects in bone mineralization are observed. For example, patients with OI type V may present with a delay in endochondral ossification, while patients with OI type VI show a defect in bone remodeling sites. Molecular studies have revealed alterations in the production and regulation of proteins such as IFITM5/BRIL and SERPINF1, which are involved in normal bone mineralization (8).

More than 1,000 heterozygous COL1A1/2 mutations have been identified. Mutation type and position influence the phenotype, and as such, genotype-phenotype relations exist to some extent (6). Generally, there's a relationship between genotype and phenotype for dominant OI caused by type I collagen genes. The molecular defect for type I OI is a null *COL1A1 allele* due to frameshifts or premature termination codons (PTCs), resulting in a decrease in the amount of structurally normal type I collagen. Splice site mutation can lead to mis-splicing with subsequent PTCs (2).

COL1A1 or *COL1A2* mutations of OI are predominated by variations in the triple-helix region. OI Mutations in N- and C-propeptide or nearby are rare and commonly patients with these terminal mutations have overlapping clinical characteristics with other syndromes (2).

5. Classifications of OI

Over time, various typologies, and classifications of OI have been proposed, highlighting the Sillence classification, established in 1979 and still in force today (Table 1).

Table 1 OI types and characteristics

OI Types	Mutation	Characteristics
Type I (OMIM: 166200)	Heterozygous mutation in COL1A 1 or COL1A 2 gene.	Bone fragility and blue sclerae, bone fractures from minimal trauma.
Type II (OMIM:166210)	Heterozygous mutation in COL1A 1 or COL1A 2 gene.	Bone fragility, perinatal fractures, severe bowing of long bones, undermineralization, death in perinatal period due to respiratory insufficiency.
Type III (OMIM: 259420)	Heterozygous mutation in one of the genes for type I collagen, COL1A 1 or COL1A 2.	Blue sclerae that normalizes with age, presents dentinogenesis imperfecta.
Type IV (OMIM: 166220)	Heterozygous mutation in COL1A 1 or COL1A 2 gene.	Easy bruising, malformations, lumbar spondylolisthesis and dentinogenesis imperfecta.
Type V (OMIM: 610967)	Heterozygous mutation in the IFITM5 gene (614757).	Calcification of the forearm interosseous membrane, radial head dislocation and hyperplastic callus formation.
Type VI (OMIM: 613982)	Homozygous mutation in the SERPINF 1 gene (172860) or in chromosome 17p13.3.	Bone fragility, low bone mass, fractures at birth, long bone deformity, ligamentous laxity, Wormian bones of the skull absence.
Type VII (OMIM: 610682)	Homozygous or heterozygous mutation in CRTAP gene (605497) or in chromosome 3p22.	Bone fragility, low bone mass, coxa vara, rhizomelia, respiratory insufficiency.
Type VIII (OMIM: 610915)	Homozygous or compound heterozygous mutation in the LEPRE1 gene (610339) on chromosome 1p32.	White sclera, severe growth deficiency, extreme skeletal undermineralization and bulbous metaphyses.
Type IX (OMIM: 259440)	Homozygous or compound heterozygous mutation in the PPIB gene (123841) on chromosome 15q22.	Bone fragility and increased susceptibility to fractures.

Type X (OMIM: 613848)	Homozygous mutation in the SERPINH gene (600943) on chromosome 11q13.	Multiple bone deformities and fractures, generalized osteopenia, dentinogenesis imperfecta, and blue sclera.
Type XI (OMIM: 610968)	Homozygous or compound heterozygous mutation in the FKBP10 gene (607063) on chromosome 17q21.	Bone fragility and low bone mass.
Type XII (OMIM: 613849)	Homozygous mutation in the SP7 gene (606633) on chromosome 12q13.	Recurrent fractures, mild bone deformations, generalized osteoporosis, delayed teeth eruption, progressive hearing loss, no dentinogenesis imperfecta, and white sclerae.
Type XIII (OMIM: 614856)	Homozygous or compound heterozygous mutation in the BMP1 gene (112264) on chromosome 8p21.	Normal teeth, faint blue sclerae, severe growth deficiency, borderline osteoporosis, and an average of 10 to 15 fractures a year affecting both upper and lower limbs and with severe bone deformity.
Type XIV (OMIM: 615066)	Homozygous mutation in the TMEM38B gene (611236) on chromosome 9q31.	Variable degrees of severity of multiple fractures and osteopenia, with normal teeth, sclerae, and hearing. Fractures first occur prenatally or by age 6 years.
Type XV (OMIM: 615220)	Homozygous or compound heterozygous mutation in the WNT1 gene (164820) on chromosome 12q13.	Early-onset recurrent fractures, bone deformity, significant reduction of bone density, short stature, and, in some patients, blue sclera.
Type XVI (OMIM: 616229)	Homozygous mutation in the CREB3L1 gene (616215) on chromosome 11p11.	Prenatal onset of multiple fractures of ribs and long bones, blue sclerae, decreased ossification of the skull, and severe demineralization.
Type XVII (OMIM: 610682)	Homozygous or compound heterozygous mutation in the CRTAP gene (605497) on chromosome 3p22.	Bone fragility and low bone mass.
Type XVIII (OMIM: 617952)	Homozygous mutation in the FAM46A gene (TENT5A; 611357) on chromosome 6q14.	Congenital bowing of the long bones, Wormian bones, blue sclerae, vertebral collapse, and multiple fractures in the first years of life.

This classification segments of OI are represented into the following types (8):

- OI type I (OMIM: 166200); it is an autosomal dominant inheritance. In most cases the null function of the alleles of COL1A 1 or COL1A 2 on chromosome 7 lead to a reduced amount of collagen I (9).
- Patients usually present with generalized osteoporosis bone fragility, persistent blue sclera for life, and deafness commencing in adolescence and young adult life. Fractures are not common in neonatal period, but it increases during childhood to puberty, decreasing thereafter, nonetheless in women it increases again after menopause and in men after the sixth decade (10). Hearing deficiency arising from both conductive and sensorineural impairment is observable in more than half of individuals diagnosed with OI type I before reaching the age of 40. Dizziness is a bothersome manifestation experienced by numerous individuals with OI type 1. Other clinical manifestations include easily bruised skin, hernias, mitral valve prolapse, aortic valvular insufficiency and large aortic root diameter. Multiple studies have documented families exhibiting autosomal dominant inheritance and variable expressivity. The occurrence rate of blue sclerae approaches nearly 100%, although the incidence of clinical fractures ranges from 90% to 95% (9). This category can be subdivided into Type IA and Type IB, depending on whether the patient also presents with dentinogenesis imperfecta, an inherited condition that affects the dentition, causing tooth fragility due to defects in the dentin, which predisposes to tooth fractures due to loss of tooth enamel support (11).
- OI type II (OMIM: 166210) is considered as the result of DNA mosaicism inherited from one of the affected patient's parents. It is characterized by extreme bone fragility, perinatal fractures, undergeneralization, severe bowing of long bones, with high perinatal mortality due to skull and thoracic fractures that can occur intrauterine or during childbirth (12).

- This mutation has 2 forms of manifestation, thin-boned and a broad bone type. One has dislocated lenses, aortic coarctation and mucoid changes, while the other one has less changes. Fetuses detected at 18-20 weeks gestation exhibit short and crumpled long bones, bending or angulation deformities in long bones, and marked deficiency of ossification in facial and cranial bones. In this early gestation period, there may be few rib fractures, but with each intrauterine month, there is progressive rib fracturing resulting in a continuously beaded appearance combined with crumpled long bones similar to an accordion. At birth, the thighs are held abducted and in external rotation. The chest size is small for gestational age, and respiratory excursion may be depressed due to pain from multiple rib fractures and abnormal biomechanical properties of continuous fracture callus thickening along each rib in severe cases. Several clinical features suggest that newborns with OI type II are in constant discomfort. They may exhibit excessive sweating, pallor, display anxiety when touched, and exhibit minimal limb movement due to multiple fractures. Approximately one-fifth are stillborn, and 90% die before reaching 4 weeks of age (9, 10).
- OI type III (OMIM: 259420). It is the result of an autosomal dominant inheritance and is associated with severe bone fragility, multiple fractures, bone fragility, skeletal deformities, blue sclerae that normalizes within the age and dentinogenesis imperfecta (12, 13).
- Patients are typically born at term with normal weight and length but may have lower limb deformities at birth. Although sclerae may be blue at birth, they tend to become less blue over time. Longitudinal growth is poor, and patients are short stature. Progressive kyphoscoliosis develops during childhood, with hearing impairment more frequent in adulthood. Radiographic studies show generalized osteopenia, multiple fractures, long bone deformities, and a characteristic "popcorn" appearance in the metaphyses. Early mortality often results from respiratory complications related to chest wall deformity. Intravenous bisphosphonate treatment has been shown to improve bone density, reduce fracture frequency, and enhance quality of life in these patients (9).
- OI type IV (OMIM: 166220). This disorder has an abnormal type of collagen I in 90% of the cases. It is an autosomal dominant inheritance; this type has a slightly higher severity than Type 1 and is characterized by white sclera or pale blue sclera. Osteoporosis and bone fragility vary in severity. Like Type 1, it can be subdivided into Type 4A and Type 4B based on the presence of dentinogenesis imperfecta (12,14).

In addition to these main categories, there are additional types of OI that do not have mutations in the genes associated with the formation of type 1 collagen (12) (Table 1):

- OI type V (OMIM: 610967) It is characterized by the formation of hypertrophic calluses after fractures, bone fragility, low bone mass, radial head dislocation, subphyseal metaphyseal radiodense line, early calcification of the interosseous membrane of the forearm and hyper dense metaphyseal bands. Unlike other types, blue sclera and dentinogenesis imperfecta are not observed. Hyperplastic callus is presented as a hard painful swelling that is localized over the bone affected (12,15).
- OI type VI (OMIM: 613982). This is a severe autosomal recessive disorder. It is distinguished by a defect in bone mineralization, nevertheless this patient doesn't present fractures at birth but during childhood they can develop long bone deformities, sclera are white or pale blue, and teeth are normal. All patients have vertebral compression fractures, wormian bones of the skull absence, osteopenia, limb deformity. As a distinctive characteristic, in the histology of iliac biopsy they have a fish-scale pattern, such as an excessive osteoid (12,16).
- OI type VII (OMIM: 610682). The CRTAP gene encodes cartilage-associated protein that is required for prolyl 3-hydroxylation of fibrillar type I and II of collagen. It is an autosomal recessive form of severe or lethal (2-3%) OI more likely to develop in the Quebec population. Patients with this type have rhizomelia shortening of the extremities, coxa vara, fractures during the birth that decrease after puberty, sclerae with minimally blue, small head circumference, eyes with proptosis and progressive deformities. Respiratory insufficiency is one of the causes of early death (12,17).
- OI type VIII (OMIM: 610915). Patients could present white sclerae, a round face, and a short barrel-shaped chest. Prenatal radiographs demonstrated gracile, undermineralized ribs and long bones. Multiple fractures were present at birth. Long bone radiographs of surviving probands showed bulbous metaphyses and apparent matrix disorganization. Their hands appeared relatively long compared to their forearms, with long phalanges, short metacarpals, and disorganized matrix. Vertebral compression fractures occurred in 2 of the surviving probands by 14 months and 5 years of age, respectively. Their bone density was lower than almost all individuals with severe OI (18).
- OI type IX (OMIM: 259440). Patients present overhydroxylation of type I collagen components over the entire length of the collagen and procollagen triple helix, suggesting overmodification of type I collagen. The transmission pattern in families is related with an autosomal recessive inheritance (19).
- OI type X (OMIM: 613848). Patients have triangular face, relative macrocephaly, bitemporal narrowing, blue sclerae, micrognathia, and relatively short limbs with bowing at the thighs. They are multiple bone deformities

and fractures that involve the upper and lower extremities and ribs and generalized osteopenia, its transmission is by an autosomal recessive inheritance (20).

- OI type XI (OMIM: 610968). Patients present a distorted lamellar structure and a fish scale-like pattern, along with elevated serum alkaline phosphatase. This type of OI could be the latter resulting from a defect in keratin-14. It is an autosomal recessive inheritance. In OI XI it can be identified homozygosity for 2 mutations: a missense mutation in the KRT14 gene known to cause EB simplex and an in-frame deletion in the FKBP10 gene causing OI. FKBP10 mutations affect type I procollagen secretion (21).
- OI type XII (OMIM: 613849). It is characterized by short stature, white sclerae, mild facial asymmetry, high prominent forehead, prominent supraorbital ridges, midface hypoplasia, prominent ears, depressed nasal bridge, microstomia, and high-arched palate. In this case SP7gene is affected and considered to be the most important because it encodes an osteoblast-specific transcription factor that had been shown in mice to be indispensable for bone formation (22).
- OI type XIII (OMIM: 614856). In these patients, fractures are result of a minimal or no trauma response, there is no abnormal quantity of calcium or phosphate, this phenotype represents a novel bone fragility disorder of moderate severity that tends to cause fracture in the lower extremities and is associated with the accumulation of osteoid due to an intrinsic mineralization defect (23).
- OI type XIV (OMIM: 615066). In this type of OI fractures occur during the pregnancy or by the age of 6 years, most of the patients have variable degrees of severity of multiple fractures and osteopenia, they don't present blue sclera, abnormal teeth and progressive hearing loss (24).
- OI type XV (OMIM: 615220). Patients with this type of OI present early-onset recurrent fractures, bone deformity, significant reduction of bone density, short stature and blue sclera, some patients could develop some brain malformations and hearing loss (25).
- OI type XVI (OMIM: 616229). This type of mutation is characterized by a homozygous mutation, nevertheless it can be presented as a heterozygous mutation, and normally in these patients, recurrent fractures with minimal trauma are exhibited as well as osteopenia and blue sclera. In this mutation, type I procollagen (COL1A1) production was normal in-patient fibroblasts, indicative of a tissue-specific effect of CREB3L1 on type I procollagen production (26).
- OI type XVII (OMIM: 610682). is an autosomal recessive form of severe or lethal OI. This type of OI doesn't present primary collagen mutations, but they have excess posttranslational modification of type I collagen, indicative of delayed folding of the collagen helix. In patients with CRTAP deficiency owing to recessive mutation, the head circumference is small, the eyes show proptosis because of shallow orbits, and the sclerae are white or light blue. Infants with CRTAP deficiency are characterized by a lack of diaphyseal modeling. Respiratory insufficiency causes early death. CRTAP mutations cause 2 to 3% of cases of lethal OI (27).
- OI type XVIII (OMIM: 617952). Patients with this type of OI usually present common fractures, they could present spontaneous fractures and vertebral collapses in the first 2 years of life also type present spontaneous fractures approximately 7 per years, dysmorphic features included high broad forehead, long eyelashes, wide palpebral fissures, blue sclerae, grooved philtrum, broad nasal root, and micrognathia (28).

In 2017, the classification of OI was supplemented based on the genetic defects present in patients. On the other hand, in 2014 another classification was introduced which, together with the Sillence classification, has been used in the detection of this disease. This last classification categorizes the phenotypes of OI into 5 groups (12) (Table 2):

- Group 1: It is characterized by being of mild severity and does not cause deformities and includes type 1 of OI (12).
- Group 2: Generally severe or lethal in severity, including type 2 OI (12).
- Group 3: Considered moderate to severe severity, with the presence of deformities, and includes types 3, 6, 8, 9, 10 and Bruck syndrome (12).
- Group 4: Classified as moderate severity, this group comprises types 4, 7, 11, 12 and 13 of OI (12).
- Group 5: Although considered moderate in severity, patients in this group have syndromes with calcification of interosseous membranes. This group includes type 5, osteoporosis-pseudoglioma syndrome, juvenile idiopathic osteoporosis, and Bruck syndrome types 1 and 2 (12).

Table 2 Clinical classification 2017

Clinical classification	Severity, phenotype	OI Type
1	Mild, non-deforming	I
2	Severe, lethal	II
3	Moderate to severe, progressive deformity	III, VI, VIII, IX, X, Sd. Bruck type 1
4	Moderate	IV, VII, XI, XII, XIII
5	Moderate, includes syndromes with calcification of interosseous membranes	V, Sd. Osteoporosis-pseudoglioma, Juvenile idiopathic osteoporosis, Sd. Bruck type 1 and 2

Recently both classifications are used, but the ones from Table 1 allows us to identify the specific type of OI as well as to identify the specific characteristics.

6. Diagnostic Approaches

The diagnosis of OI is usually based primarily on clinical evaluations, using the classification previously described by Sillence. The findings and severity of disease in a specific patient are determined by considering four main variables (29):

- Clinical Evaluation: This includes the history of fractures, the presence of deformities, growth retardation, blue sclera, dentinogenesis imperfecta or other relevant signs. In addition, family history is analyzed to identify hereditary patterns (29).
- Radiological Findings: Radiological studies help detect fractures, osteopenia, callus formation, bone density and mineralization, among other aspects relevant to diagnosis (29).
- Skin biopsy: Skin biopsy can help confirm the diagnosis by looking at a different pattern of type I collagen. However, its efficacy may be limited, as in certain mutations, this difference in collagen may be bone-specific and not evident in the patient's skin (29).
- Biochemical Markers: These biochemical indicators are useful for assessing bone formation or resorption. Importantly, in most cases of OI, bone resorption prevails (29).
- Bone Densitometry: This study allows the evaluation of bone mineral content. In mild cases of the disease, bone density may be normal, but in more severe forms, it tends to decrease significantly (29).
- Bone Biopsy: This procedure provides detailed information on the morphological and ultrastructural alterations of bone tissue, facilitating the accurate classification of the type of OI present in the patient (29).

Elucidating the disease-causing mutation is useful in patients who have a clinical diagnosis of OI, as it provides information about the risk of recurrence in a family and allows for the identification of affected family members. Genetic testing can also have implications for clinical management. For example, finding the OI type V specific *IFITM5* mutation indicates that the patient has a high risk of developing hyperplastic callus, radial head dislocation, and abnormalities in the craneo–cervical junction. Mutations affecting the C-propeptide of the collagen type I alpha 1 chain are frequently associated with hip dysplasia, and glycine substitutions caused by mutations in exon 49 of *COL1A2* may predispose to intracranial hemorrhage (30).

Genetic testing can also be useful when the diagnosis is not obvious from the clinical picture. For example, it can sometimes be difficult to distinguish OI type I from other causes of recurrent fractures in children and adolescents. This situation was investigated in a study of 94 individuals less than 21 years of age who had a significant fracture history (one or more long-bone fracture of the lower extremities, two or more long-bone fractures of the upper extremities, one or more vertebral compression fracture: all in the absence of major trauma), but had white sclera and no signs of dentinogenesis imperfecta; therefore, they did not have unequivocal signs of OI. Sequence analysis of a panel of OI-associated genes found disease-causing mutations in 26 (28%) of these individuals. Hence, a proportion of children and adolescents with recurrent fractures have OI even if the family history is negative and the phenotypic appearance does not clearly suggest a diagnosis of OI (30).

Genetic testing is essential for the identification of pathogenic variants, inheritance pattern, and differential diagnosis. Based on the clinical and radiographic features, and family history either the sequencing of COL1A1 and COL1A2 or a

comprehensive next-generation sequencing panel (all OI genes and genes associated with skeletal dysplasia) is initially recommended. The interpretation of genetic testing results can sometimes be challenging: Identifying unknown significance variants, or sequence variants in a new gene (not previously reported in OI cases). Genotype-phenotype correlations are sometimes difficult to establish, due to the wide OI phenotypic variability, in association with genetic or epigenetic modifiers (31).

The therapeutic approach for OI is primarily aimed at reducing the incidence of fractures, improving pain, promoting adequate growth, and promoting the patient's mobility and functional independence. To achieve an effective treatment against this disease, it is essential to work in collaboration with various medical disciplines. Orthopedic surgery deals with the management of fractures and the surgical correction of deformities in the long bones and spine. Physical therapy plays a crucial role in patient motor development, pain relief, and promotion of functional independence. Intervention by dentists and nutritionists is also essential to maintain adequate levels of vitamin D and calcium, both of which are critical for bone health and to minimize the side effects of bisphosphonate use (32).

Growth hormone has been considered as a therapeutic option to address growth deficiency in patients with OI. Studies in patients with type IV OI suggest that treatment with growth hormone may increase cancellous bone density, and a synergistic effect has been observed when combined with bisphosphonate therapy on growth velocity. However, there is currently insufficient evidence to support its use as part of standard treatment for OI (32).

Nitrogen bisphosphonates, such as pamidronate, alendronate, risedronate and zoledronic acid, are currently considered the most effective pharmacological option in pediatric patients, as they increase bone mass and reduce the risk of fractures. Intravenous administration of bisphosphonates is preferred over the oral route, as it has been shown to improve bone density and reduce fractures more effectively, as well as minimizing associated side effects (32).

7. Conclusion

In conclusion, OI, also known as brittle bone disease, is an inherited connective tissue disorder caused by mutations in type I collagen genes. Perhaps most striking is the profound impact this condition can have on the quality of life of those who experience it. From the constant risks of fractures to skeletal deformities and associated complications, every day can be a battle. The extensive range of mutations identified in these genes, exceeding 1,000 variants, presents a challenge in genotype-phenotype correlation. Nevertheless, some relationships have been established. Furthermore, the inclusion of new classifications and subtypes based on more recent genetic and clinical findings has enriched our understanding of the heterogeneity of the disease.

The advent of next-generation sequencing panels has facilitated the identification of mutations even in cases where the clinical presentation is not typical. Furthermore, the continued advancement of molecular genetics and developmental biology research is essential for the discovery of novel therapeutic targets and the improvement of therapeutic approaches for OI. A more profound comprehension of the molecular mechanisms underlying this disease may pave the way for more targeted and efficacious interventions that address both bone symptoms and associated systemic complications.

Ultimately, an approach to OI from a genetic perspective not only expands our knowledge of the disease, but also opens new avenues for more precise and personalized management of affected patients.

To accurately diagnose OI, a comprehensive evaluation is required, which should include genetic, radiological and clinical testing.

The identification of pathogenic mutations provides crucial information for clinical management and genetic counseling, as well as influencing patient prognosis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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