Review

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Osteogenesis imperfecta: shifting paradigms in pathophysiology and care in children

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Abstract: The formation of functional bone requires a delicate interplay between osteogenesis and osteolysis. Disturbances in this subtle balance result in an increased risk for fractures. Besides its mechanical function, bone tissue represents a key player in the regulation of calcium homeostasis. Impaired bone formation results in bone fragility, which is especially pronounced in osteogenesis imperfecta (OI). This rare genetic disorder is characterized by frequent fractures as well as extraskeletal manifestations. The current classification of OI includes 23 distinct types. In recent years, several new mutations in different genes have been identified, although the exact pathomechanisms leading to the clinical presentation of OI often remain unclear. While bisphosphonates are still the standard of care, novel therapeutic approaches are emerging. Especially, targeted antibody therapies, originally developed for osteoporosis, are increasingly being investigated in children with OI and represent a promising approach to alleviate the consequences of impaired osteogenesis and improve quality of life in OI patients. This review aims to provide insight into the pathophysiology of OI and the consequences of distinct disease-causing mutations affecting the regulation of bone homeostasis. In this context, we describe the four most recently identified OI-causing genes and provide an update on current approaches for diagnosis and treatment.

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Introduction

Although typically regarded as a rare condition, the prevalence of osteogenesis imperfecta (OI) is estimated to be 1:10.000, making it one of the most common skeletal diseases in children [1]. The clinical picture was already documented in 1788 by the Swedish physician Olaus Jakob Ekman [2]. However, significant advances in understanding the pathophysiology of OI were first made in the 1980s, when mutations in *COL1A1* and *COL1A2*, coding for the distinct chains of the triple helical collagen type I, were identified as the primary disease-causing genes [3]. Quantitative and structural defects of collagen type I, the critical component of the bone matrix, result in increased bone fragility and a predisposition to fractures after minor trauma. Initially thought to be a monogenic disorder, it is now known that OI involves a broad spectrum of genes, most of them involved in the synthesis of collagen I. The original classification of OI, introduced by David Sillence in 1979, categorized the disease into four types based on clinical severity: Type I (mild), Type II (perinatal lethal), Type III (severe with significant skeletal deformities), and Type IV (moderate severity) [4]. An alternative, genetic classification was implemented in the last years that defined each OI type based on the affected gene. This classification includes to date 23 different types, which reflects the complexity of this continuously growing field [5]. This review will give a brief overview of the underlying pathophysiology including the four most recently identified OI-causing genes. The focus, however, will be on the clinical aspects of OI, including the clinical presentation, diagnostic approaches, and management strategies.

Pathophysiology of OI

The human skeleton is a dynamic organ, constantly undergoing remodeling through the coordinated actions of bone

formation and resorption. This remodeling process allows bones to repair microdamage, respond to changes in mechanical load, and ensure that old or damaged bone is replaced by new, stronger bone tissue [6]. Additionally, dynamic remodeling is essential for maintaining stable extracellular calcium levels needed for various physiological functions such as muscle contraction, enzymatic activity, and neuronal signaling.

Bone metabolism is regulated by three cell types: osteoblasts, osteoclasts, and osteocytes. Osteoblasts, derived from mesenchymal stem cells, are responsible for synthesizing new bone matrix and facilitating mineralization. Once osteoblasts become embedded in the matrix, they differentiate into osteocytes, which act as mechanosensors and regulate bone remodeling. Osteoclasts, on the other hand, are derived from hematopoietic stem cells and resorb bone [7].

The bone forming activity of osteoblasts and bone resorption by osteoclasts is tightly regulated. Mechanical loading, hormones (e.g., growth hormone, PTH, and estrogen), nutritional factors, along with local cytokines and growth factors, regulate this complex balance. Muscle activity plays a critical role in bone remodeling by generating mechanical forces that stimulate bone formation. Osteocytes detect mechanical strain through their dendritic processes within the bone matrix and transduce these signals into biochemical responses [8].

The signaling pathways regulating bone metabolism are highly complex, and a comprehensive discussion is beyond the scope of this review. However, some are essential to understand, as they have already been targeted by pharmacological therapies currently under investigation for the use in OI. These pathways include the Wnt/β-catenin, RANK/RANKL/OPG, and TGF-β pathway.

The Wnt/β-catenin signaling pathway is crucial for promoting osteoblast differentiation and activity. Wnt ligands bind to the transmembrane receptor “Frizzled” and its coreceptor, the low-density lipoprotein receptor–related protein –5 or –6 (LRP5/6) receptors on osteoblasts, leading to β-catenin stabilization and translocation to the nucleus, stimulating the transcription of genes involved in bone formation [9]. Sclerostin, a protein produced by osteocytes, binds to the LRP5/6 receptor and disrupts its interaction with Wnt proteins, thereby acting as a negative regulator of osteoblast activity and bone formation [10]. The RANK/RANKL/OPG pathway plays a key role in osteoclast regulation. RANKL (Receptor Activator of Nuclear Factor κB Ligand), produced by osteoblasts and osteocytes, binds to its receptor RANK on osteoclast precursors, promoting their maturation and activation [11, 12]. Osteoprotegerin (OPG), a secreted decoy receptor for RANKL, is produced by osteoblasts and can inhibit this interaction. TGF-β has a context-dependent effect on bone formation and absorption and interacts with the RANKL pathway. Upon binding to its receptors on osteoblast precursors, TGF-β triggers SMAD proteins, which translocate to the nucleus to upregulate expression of collagen and other components of the extracellular matrix. However, in certain conditions where increased bone resorption is required, TGF-β can enhance the expression of RANK on the surface of osteoclasts and bone marrow stromal cells, thereby promoting osteoclast differentiation and activity [13, 14].

A disruption of this complexly balanced system of bone formation and resorption can cause various bone disorders characterized by impaired bone stability. In osteoporosis, a condition which is commonly seen in elderly woman, a decline in estrogen levels after menopause causes an increased osteoclast activity and loss of bone mass [15]. Conversely, disturbances of the structural composition of bone can also impair its stability. OI is a genetic disorder, primarily caused by quantitative or qualitative defects of collagen I, the main structural protein of most connective tissue in the human body, making OI a multisystemic disease.

OI as a collagen I–related disorder

Collagen I is the primary organic component of bone matrix. It provides a scaffold for mineral deposition and imparts tensile strength to the bone. Collagen I is primarily synthesized by osteoblasts and fibroblasts and undergoes extensive post-translational modifications within the endoplasmic reticulum (ER). Assembled into a stable triple-helical structure, the procollagen chains are secreted into the extracellular matrix. Intra- and intermolecular crosslinks provide mechanical strength of collagen fibers [16].

Mutations in *COL1A1* and *COL1A2* can lead to OI with a broad phenotypic variety, ranging from mild to perinatal lethal, depending on the specific type of mutation. Mutations such as stop mutations or frameshift mutations can introduce a premature stop codon into the mRNA. In many cases, this leads to nonsense-mediated decay, and no collagen is produced from the mutated allele, resulting in a quantitative collagen deficiency. However, in heterozygous patients, the presence of one normal allele allows for partial compensation, typically leading to a milder phenotype [4].

In contrast, missense mutations that affect glycine residues essential for the proper folding of the triple-helix cause a more severe phenotype. Misfolded collagen is incorporated into the extracellular matrix, where it forms defective collagen fibrils that stimulate bone resorption by osteoclasts. Furthermore, intracellular accumulation of structurally abnormal collagen causes cellular stress, chronic low-grade inflammation, and osteoblast apoptosis [17].

While mutations in *COL1A1* and *COL1A2* are the most common causes of OI, there are several other genes involved in various processes related to collagen production, post-translational modification, bone formation, and mineralization that can lead to different forms and severities of OI when mutated. In addition to genes causing classical OI, some mutations result in phenotypes that exhibit bone fragility similar to OI, but these conditions may historically be categorized under other syndromes with overlapping features. These are often referred to as "OI-like phenotypes." A detailed overview of all genes associated with OI and OI-like phenotypes is provided in Table 1.

Table 1: Summary of genes and phenotypic characteristics of OI and OI-like phenotypes.

Category	Affected pathway	Affected gene (mode of inheritance)	Protein	Characteristics and phenotype	Genetic OI type	OMIM
Collagen synthesis and modifications	Collagen synthesis	*COL1A1* *COL1A2* (AD)	Pro-alpha 1(I)/pro-alpha 2 (I) chain of type I collagen	– Up to 90 % of all OI cases – Mild to moderately deforming to severe – Perinatal lethal forms (type II) [4] – Stop-mutations usually milder phenotype [5]	I II III IV	166200 166210 259420 166220
	mRNA stabilization	*TENT5A* (AR)	Terminal nucleotidyl-transferase 5A (TENT5A) alternative: family with sequence similarity 46, member A (FAM46A)	– Severe OI – Decreased body length, skull deformities, reduced cortical thickness [18]	XVIII	617952
	Hydroxylation of proline and lysine residues	*P4HB* (AR)	Protein disulfide isomerase (PDI) alternative: prolyl 4-hydroxylase subunit beta (P4HB)	– Cole–Carpenter syndrome[b] [19]	Not classified	112240
		CRTAP (AR)	Cartilage-associated protein (CRTAP)	– Cole–Carpenter syndrome[b] [20] – Severe to lethal OI[21]	VII	610682
		P3H1 Alternative: *LEPRE1* (AR)	Prolyl-3-hydroxylase 1 (P3H1)	– Severe to lethal OI [22, 23]	VIII	610915
		PPIB (AR)	Peptidyl-prolyl-cis-trans-isomerase B (PPIB) alternative: cyclophilin B	– Moderate to severe OI [24, 25] – Lethal [26]	IX	259440
	Chaperone-assisted formation of procollagen triple helix and quality control	*SERPINH1* (AR)	Serpin peptidase inhibitor, clade H, member 1 alternative: heat shock protein 47 (HSP47)	– Moderate to severe OI – Blue sclerae – Dentinogenesis imperfecta [27, 28]	X	613848
		FKBP10 (AR)	Peptidyl-prolyl cis-trans isomerase FKBP10 (PPIase FKBP10) alternative: 65 kDa FK506-binding protein (FKBP65)	– Bruck syndrome[e] type 1 [29–31]	XI	610968
		KDELR2 (AR)	(Lys-Asp-Glu-Leu) endoplasmic reticulum protein receptors 2 (KDELR2)	– Severe OI with perinatal fractures [32, 33]	XXI	619131
	ER homeostasis	*CREB3L1* (AR)	Cyclic AMP-responsive element-binding protein 3-like protein 1 (CR3L1)	– Moderate to severe OI – Prenatal fractures and shortening of long bones – Milder phenotype in heterozygous forms [34]	XVI	616229
		MBTPS2 (XLR)	Membrane-bound transcription factor site-2 protease alternative: endopeptidase S2P	– Moderate to severe OI [35] – IFAP syndrome with or without BRESEK or BRESHECK[a] – Olmsted syndrome[d]	XIX	301014

Table 1: (continued)

Category	Affected pathway	Affected gene (mode of inheritance)	Protein	Characteristics and phenotype	Genetic OI type	OMIM
		TMEM38B (AR)	Transmembrane protein 38B (TMEM38B) alternative: trimeric intracellular cation channel type B (TRIC-B)	– Mild to severe OI – Hypotonia – Cardiac abnormalities [36]	XIV	615066
	Vesicular transport to Golgi apparatus and extracellular space	*SEC24D* (AR)	Selected protein acidic and rich in cysteine (SPARC)	– Cole–Carpenter syndrome[b] [37]	Not classified	616294
	Extracellular proteolytic processing and conversion into mature collagen	*BMP1* (AR)	Bone morphogenic protein 1 (BMP1)	– Moderate to severe OI – Macrocephaly – High BMD, reduced trabecular numbers, and increased bone porosity [38, 39]	XIII	614856
	Collagen crosslinking	*PLOD2* (AR)	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (PLOD2) alternative: lysyl hydroxylase 2 (LH2)	– Bruck syndrome type 2[e] [40, 41]	Not classified	609220
Bone homeostasis	ECM mineralization	*SPARC*[c]	Selected protein acidic and rich in cysteine (SPARC)	– Moderate to severe OI – Delayed motor development – Brain MRI abnormalities [42]	XVII	616507
	Transduction of mechanical stimuli on osteocytes	*PLS3* (XLD)	Plastin-3 (PLS3)	– Low bone turnover OI – Osteoarthritis – X-linked osteoporosis in adults [43]	Not classified	300910
	Regulation of osteoblast differentiation or function and collagen synthesis	*WNT1* (AR)	Proto-oncogene Wnt1 (wingless-type MMTV integration site family, member 1, WNT1)	– Severe OI – Developmental disorders and cognitive impairment [44–46]	XV	615220
		MESD (AR)	Mesoderm development LRP chaperone (MESD)	– Progressively deforming to lethal OI [47] – Oligodontia – Intellectual disability [48, 49]	XX	618644
		TAPT1 (AR)	Transmembrane anterior posterior transformation 1 (TAPT1)	– Severe, progressively deforming OI [50] – Lethal osteochondrodysplasia with ciliopathy [51]	Not classified	616897
		SP7 (AR, AD)	Transcription factor Sp7 alternative: zinc finger protein osterix	– Moderate to severe OI [52] – Sclerotic skeletal dysplasia with low bone turnover [53] – Hearing impairment [54]	XII	613849
	Regulation of osteoclast differentiation or function	*SERPINF1* (AR)	Pigment epithelium-derived factor (PEDF)	– Progressively deforming OI – Increased osteoclastic activity with poor response to bisphosphonates [55, 56]	VI	613982
		IFITM5 (AR)	Interferon-induced transmembrane protein 5 (IFITM5) alternative: bone-restricted interferon-induced transmembrane protein-like protein (BRIL)	– Moderate to severe OI – Hyperplastic callus formation – Ossification of interosseous membrane of forearms and lower legs – Radial head dislocation [57]	V	610967

Table 1: (continued)

Category	Affected pathway	Affected gene (mode of inheritance)	Protein	Characteristics and phenotype	Genetic OI type	OMIM
		CCDC134 (AR)	Secreted coiled-coil domain containing protein 134	– Severe OI – Potential overlap with other skeletal dysplasias with dysregulated MAPK/ERK signaling (Noonan syndrome, neurofibromatosis type 1, cardiofaciocutaneous syndrome [58, 59] – Poor response to bisphosphonate therapy [60]	XXII	619795
Unknown	Unknown	*PHLDB1* (AR)	Pleckstrin homology-like domain, family B member 1	– Moderate to severe OI – Platyspondyly – Widened metaphyses – Insulin resistance [61]	XXIII	620639

AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive; XLD, X-linked dominant; BMD, bone mineral density. [a] IFAP: ichthyosis follicularis, alopecia, photophobia. BRESEK: bronchiectasis, restrictive pulmonary disease, encephalopathy, skeletal contractures, and ichthyosis. BRESHECK: brain anomalies, ectodermal dysplasia, skeletal malformations, and cryptorchidism. [b]Cole–Carpenter syndrome is an OI-like syndrome with bone fragility, craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features (frontal bossing, midface hypoplasia, micrognathia) [20]. Type I and II exist, differentiation based on genetic findings. [c]SPARC has a function as a chaperone for collagen folding and is also involved in ECM mineralization. [d]Olmsted syndrome is a rare keratinization disorder characterized by palmoplantar keratoderma and perioral keratotic plaques [62, 63]. [e]Bruck syndrome is characterized by bone fragility, osteoporosis, and congenital joint contractures. Two types exist classified based on genetic finding.

Novel genetic insights from inherited bone fragility syndromes

Over the last years, genetic analyses of patients with the clinical phenotype of OI led to the discovery of novel genes. The list of OI types has been updated accordingly and currently ends with type XXIII [5]. However, not all newly identified genes have been officially classified as distinct OI types. In the following section, the four latest described genes and the function of the encoded proteins are briefly summarized.

KDELR2 (OI type XXI)

In 2020, three different mutations in *KDELR2 (KDEL receptor 2)* were first identified in six affected individuals from four families [32]. Later, another two missense variants were reported. All affected individuals had been diagnosed with progressively deforming OI or OI type II; in the latter cases, additional neurodevelopmental features were reported [33]. *KDELR2* encodes for a seven transmembrane domain receptor that localizes mainly to the ER, the intermediate ER–Golgi compartment, and the cis-Golgi complex indicating a crucial function in the secretion of proteins. KDELR2 binds proteins harboring a KDEL-like motif and regulates their trafficking between compartments. Interestingly, the collagen chaperone heat shock protein 47 (Hsp47) is one of the substrates and KDELR2 mutations lead to a reduction of intracellular levels and an increased secretion of Hsp 47. Finally, this results in impaired extracellular collagen fibril formation [32].

CCDC134 (OI type XXII)

Whole exome sequencing of three Moroccan patients from two families with severe OI identified a homozygous missense mutation in the first codon of *CCDC134* [58]. Later, a male infant [60] and a Brazilian boy with severe OI harboring exactly the same mutation were described [59]. The gene encodes for the secreted coiled-coil domain containing protein 134 that is involved in the transcriptional regulation and signal transduction of MAP kinases. The mutation causes a loss of protein function and the pathomechanisms might involve a dysregulated MAPK/ERK signaling in osteoprogenitors. However, the exact mechanism as well as the overlap with other bone dysplasias with dysregulated MAPK/ERK signaling is not yet fully understood.

PHLDB1 (OI type XXIII)

In 2023, a new mild OI phenotype with regressive spondylometaphyseal alterations was reported in five infants from two unrelated families. In both families, the parents of the affected individuals were first cousins [61]. Two biallelic

frameshift variants were identified in the candidate gene *PHLDB1* that encodes the protein Pleckstrin homology-like domain, family B, member 1. The frameshift mutations lead to the loss of the C-terminal PH domain. The function of PHLDB1 is largely unknown. It interacts with and is a modulator of the Akt protein kinase [64], and it was suggested that this interaction might affect collagen biosynthesis or osteogenic differentiation [61].

TAPT1

Mutations in the gene *TAPT1* were first reported to result in a complex and early osteochondrodysplasia with features of lethal OI in two consanguineous families from Morocco and Syria [51]. In 2023, two groups independently described novel homozygous mutations in *TAPT1* in seven patients from consanguineous families that survived and were clinically diagnosed with OI [65, 66]. The function of the encoded protein TAPT1 (transmembrane anterior posterior transformation 1 protein) is not yet completely understood, but mutations led to a disrupted ciliogenesis and an altered morphology of the Golgi apparatus that might affect collagen secretion [51]. Molecular analysis also revealed an impaired collagen fibril formation that might explain brittle bones [66]. Currently *TAPT1* is not yet classified as an OI-causing gene.

Clinical presentation

Osteogenesis imperfecta presents with a wide spectrum of clinical manifestations, ranging from mild to severe, depending on the specific type of OI and the underlying genetic mutations. While some infants present with multiple fractures already at birth, others remain asymptomatic until fractures occur later in childhood, often after they start walking. While early medical and physiotherapeutic interventions can help those with mild to moderate forms to maintain mobility, more severely affected individuals are typically wheelchair dependent throughout life.

Fractures occur typically in the long bones of the upper and lower extremities as well as in vertebrae and can lead to severe skeletal deformities, such as bowed limbs and scoliosis (Figure 1). Thorax deformities can restrict lung expansion and impair respiratory function [67]. In severe cases, scoliosis may cause neurological complications due to compression of the spinal cord [68, 69]. Basilar invagination is a condition more commonly observed in severe forms of OI, where recurrent microfractures cause the skull base to flatten, leading to spine migration into the skull [70]. This can compress the brainstem and cerebellum, causing hydrocephalus due to disrupted cerebrospinal fluid circulation and cranial nerve damage. Early screening for new neurological symptoms is crucial. Growth is often affected due to disruptions in the growth plates, reflecting the disease's profound impact on bone development [71]. Repeated immobilization following fractures contributes to muscle atrophy and secondary bone loss, further aggravating bone fragility. Chronic pain is often underrecognized by parents and caregivers and consequently insufficiently managed [72]. This significantly impacts quality of life in children and adolescents with OI, as highlighted by the recently published IMPACT survey, which documented experiences of individuals with OI and their caregivers [73, 74].

Extraskeletal manifestations

Due to the widespread role of collagen I in various tissues, OI also presents with different extraskeletal manifestations (Figure 2). Characteristic facial features like a triangular face shape, blue sclerae, and brittle and discolored teeth (dentinogenesis imperfecta) can provide diagnostic indicators [75, 76]. Neurodevelopmental delay indicate the possibility of OI type XV, a form associated with cognitive impairment caused by mutations in *WNT1* [77].

Other manifestations usually appear in adulthood and are, therefore, in most cases not relevant for the diagnosis but need to be considered by the medical team and care takers as they have significant impact on the patient's quality of life. Fragility and deformation of the ossicles in the middle ear, as well as the abnormal remodeling of the otic capsule in the inner ear, can cause early hearing loss [78]. Abnormalities in collagen fibers can affect the structural integrity of heart valves and blood vessels, potentially leading to cardiovascular complications such as valve insufficiency and increased susceptibility to aortic dilation or rupture [79]. Thoracic deformities and intrinsic defects in the lung parenchyma restrict lung expansion and function [67]. In OI type II, the most severe type, prenatal rib fractures and underdeveloped lungs lead to respiratory failure and usually cause death in the perinatal period [80].

Diagnosis

To confirm the diagnosis of OI, a combination of clinical evaluation, imaging, and genetic testing is typically required. Importantly, not all patients exhibit the full spectrum of symptoms and individuals with milder forms may be misdiagnosed with conditions like juvenile osteoporosis or

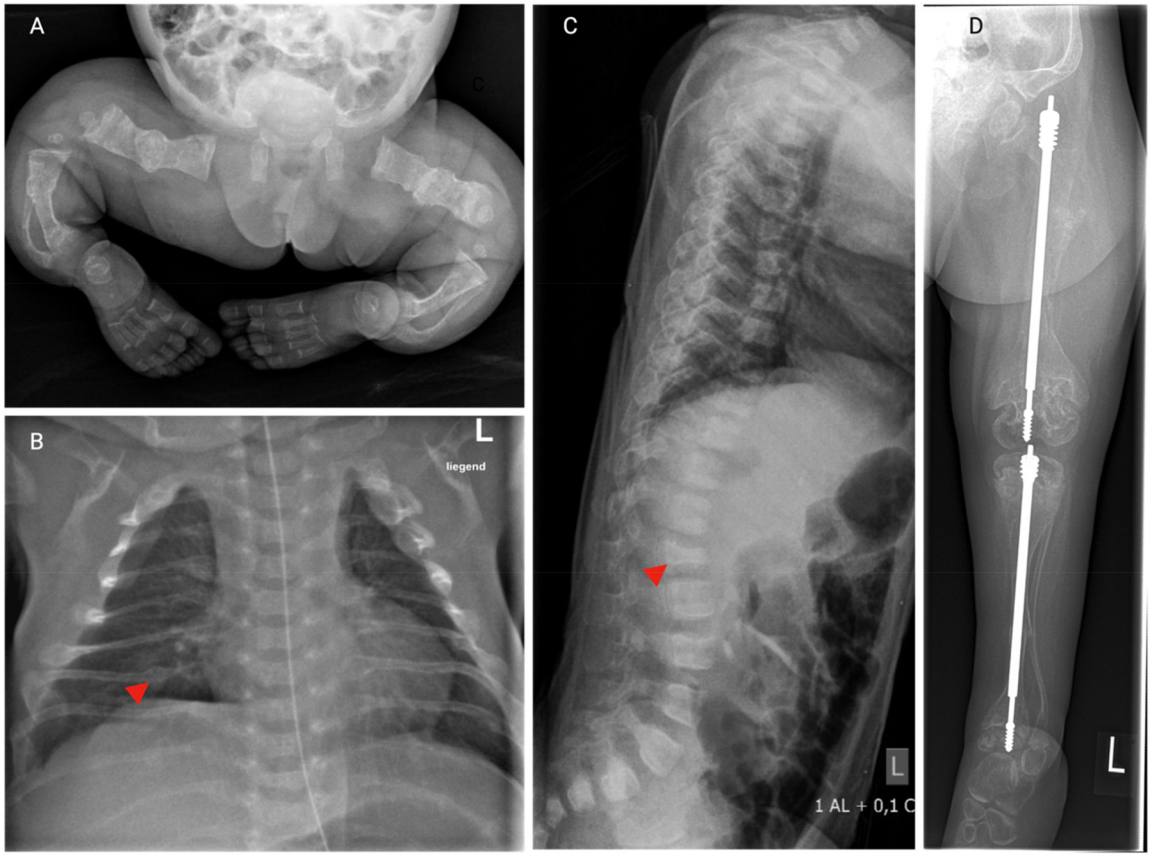

Figure 1: Skeletal manifestations of OI. Series of X-rays from a young girl with severe OI type VIII. (A) X-ray of the lower body 3 days after birth showing multiple healed fractures, generalized osteopenia, bowing and shortening of the long bones. (B) Chest X-ray 3 days after birth. Notice the thin rips with irregularly shaped, thickened areas (arrow head) consistent with healed fractures. (C) Lateral X-ray of the spine in the age of 1.5 years reveals flattened, irregularly shaped vertebral bodies (arrow head), indicative of compression fractures, along with pronounced kyphosis. (D) X-ray of the lower extremity in the age of 5 years after surgical insertion of telescopic nails in the tibia and femur. Notice the generalized osteopenia, thin cortical bones, multiple fractures in the tibia and femur, and bowing of the thin fibula. The distal metaphyses of the femur appear wide and irregular.

remain undiagnosed until adulthood. However, certain clinical signs should raise suspicion of OI. Children typically present with recurrent fractures without a clear cause or with an injury disproportionate to the reported trauma, a constellation of symptoms that often alerts clinicians and raises suspicion of child abuse.

Like other monogenetic diseases, a detailed family history might pave the way to the correct diagnosis. Recurrent fractures in one parent can guide the physician in the direction of OI, although not all patients have a positive family history, as spontaneous mutations are common [81].

Radiographic imaging is often the first diagnostic tool, revealing generalized osteopenia, multiple fractures at different stages of healing and bone deformities. Wormian bones are extra bone pieces that occur particularly along the lambdoid suture. So-called popcorn calcifications are disorganized hyperdense lines around the metaphyseal growth plates of long bones [82, 83]. The measurement of bone density via dual-energy X-ray absorptiometry (DXA) scans plays a supporting role in the diagnosis of OI. It does not help to differentiate OI from other bone diseases like osteoporosis, but it remains an important tool for monitoring effectiveness of antiresorptive treatments.

Laboratory diagnostics including measurements of calcium, phosphate, alkaline phosphatase (AP), vitamin D, and parathyroid hormone levels are recommended to exclude metabolic bone disorders associated with increased bone fragility, such as nutritional rickets or X-linked hypophosphatemia [81].

Genetic testing is currently gaining more and more relevance and the number of identified genes contributing to the OI phenotype is continuously growing. Genetic and phenotypical overlap with other connective tissue disorders, such as Ehlers–Danlos syndrome and Bruck syndrome, make the classification of patients into distinct diagnostic categories increasingly challenging [84]. For diagnosing OI, genetic testing is not mandatory. However, the deeper understanding of the genetic background and pathophysiology

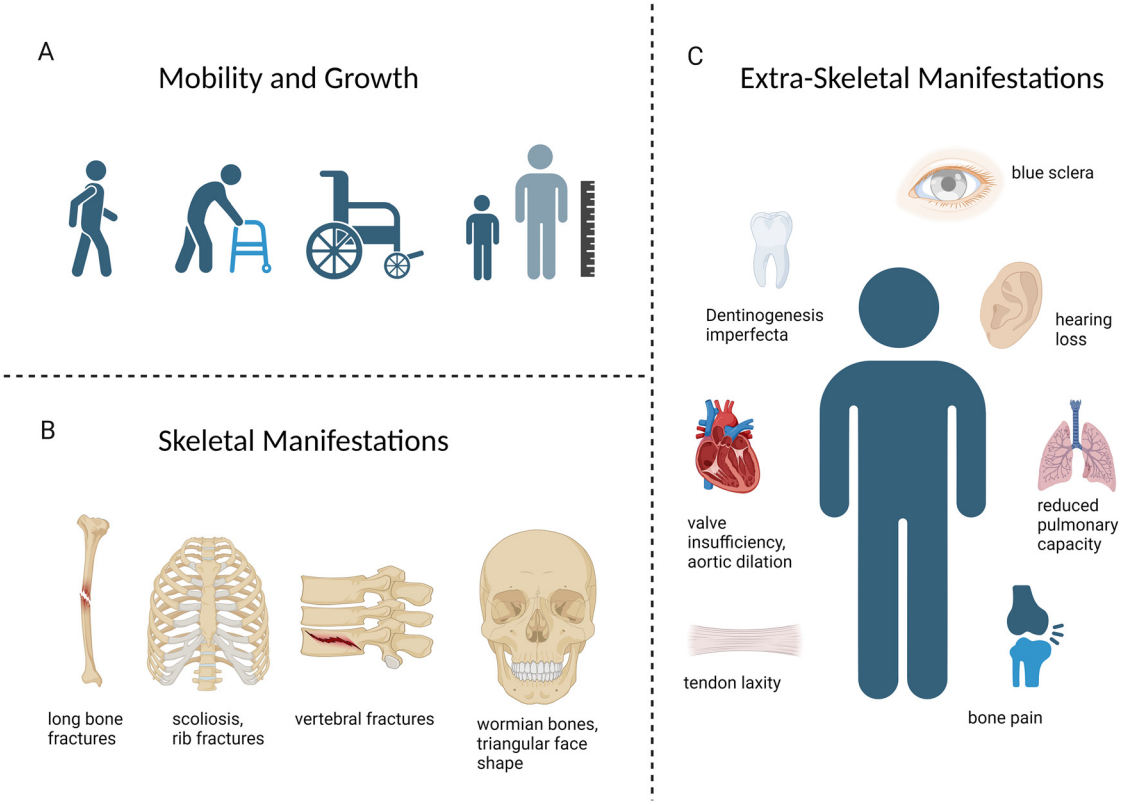

Figure 2: Clinical manifestations of OI. (A) The phenotype of OI ranges from patients with mild forms who maintain full mobility, to those who rely on walking aids or are wheelchair dependent. Short stature is commonly present. (B) Skeletal manifestations of OI include fractures and deformities of the long bones, scoliosis, vertebral fractures, and craniofacial features like wormian bones, and a characteristic triangular face shape. (C) Extraskeletal manifestations occur due to the widespread presence of collagen I in various organ systems. Structural abnormalities in heart valves, blood vessels, and the lung parenchyma can restrict cardiopulmonary function and cause potentially lethal complications. Blue sclera and dentinogenesis imperfecta are characteristic facial features. Early-onset hearing loss and ligamentous laxity can also occur.

of OI resulted in a paradigm shift in the approach to manage this condition, as patients are no longer treated as one homogenous group. Instead, with the increasing knowledge of the disease's pathophysiology, more targeted therapeutic strategies are currently investigated.

Management and therapy

The management of OI is primarily focused on symptomatic and supportive care, as there is currently no curative treatment available. A multidisciplinary approach (Figure 3) involving pediatricians, orthopedic surgeons, physiotherapists, and many other disciplines is essential to account for the complex needs of OI patients [81, 85]. Patients with OI and their caregivers, including health care professionals, often develop a fear of injuries and fractures [86]. Parents and hospital staff should, therefore, be trained how to handle OI patients safely from birth on. Overprotection due to fear of fractures impairs the social and motor development of the child. Therefore, education of the caregivers is a key component of the multidisciplinary treatment approach [87]. Psychological support and patient support groups can help patients and their families coping with fears and challenges of living with a chronic condition.

Orthopedic management involves acute fracture treatment and the correction of chronic bone deformities. Fractures are usually treated by immobilization (casts, splints, bandages) while severe deformities and dislocated fractures require surgical interventions. Telescopic intramedullary rods, which prolong as the child grows, offer long-term stability and help maintain bone alignment [88]. Spinal surgery is indicated for progressive spinal deformities to correct misalignments, improve respiratory function, relieve pain through neural decompression, and enhance spinal stability [68, 69]. Concerns about potential side effects and lack of standardized pain assessment in young children often lead to insufficient pain management in chronically ill children

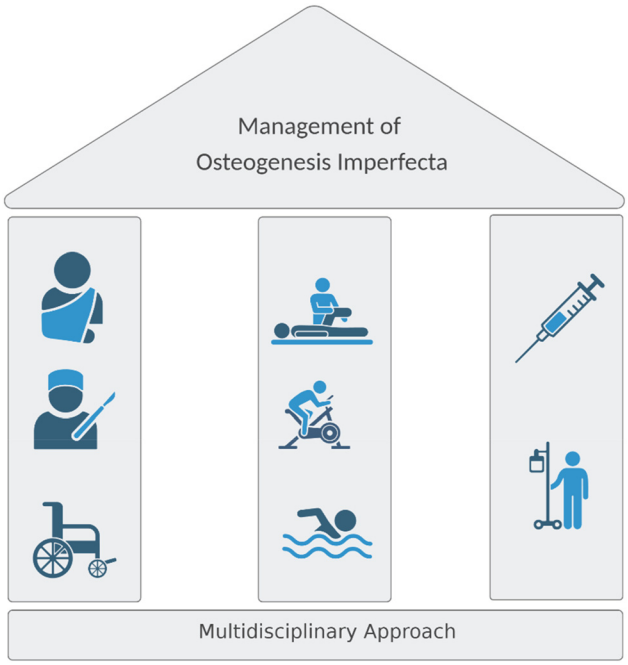

Figure 3: The three pillars of OI therapy. The multidisciplinary approach for OI patients includes physiotherapy, orthopedic management of acute fractures, and surgical correction of deformities and pharmacological therapy. Psychological support should always be provided to help the family managing a chronic, life-long condition.

[74, 89]. However, adequate pain management is essential to prevent immobilization due to fear of new fractures; therefore, its effectiveness should be evaluated regularly.

Physiotherapy plays a key role in enhancing mobility, motor function, and independence in daily activities [87]. Rehabilitation should aim to reduce the risk of fractures and deformities, while allowing the child to safely engage in activities that promote development. Especially after fractures, it is important to prevent contractures and joint misalignment and reduce secondary osteopenia from immobilization. Exercises focusing on improving muscle strength, coordination, and endurance are essential. Weight-bearing activities, isometric exercises, and functional training can significantly improve walking ability and bone mineral density (BMD) in OI patients [90]. Specific physiotherapy modalities exist for OI patients that provide a low-impact environment and minimize the risk of injury, such as whole-body vibration training and aquatic physiotherapy [87, 91].

Pharmacological treatment approaches

The pharmacological management of OI focuses on two primary therapeutic strategies: antiresorptive and osteoanabolic therapies. Both approaches have been adapted from treatments commonly used in adults with osteoporosis, although their application in OI and in children remains largely under investigation. An overview of the current medical treatment approaches is provided in Figure 4.

Antiresorptive drugs

Bisphosphonates

Bisphosphonates, first introduced as a pharmacological treatment for children with OI in the 1980s, still remain the standard of care [81, 92]. These compounds bind to hydroxyapatite crystals in bone and are internalized by osteoclasts upon their activation and attachment to the bone surface. Once internalized, bisphosphonates disrupt key metabolic pathways within the osteoclasts, leading to functional inhibition or apoptosis, thereby reducing bone resorption. This results in increases of bone mass, reduced incidence of vertebral compression fractures and bone pain, and vertebral remodeling [93]. While generally well tolerated, short-term side effects include flu-like symptoms, such as fever, bone pain, and fatigue [94]. Oral administration of bisphosphonates may cause gastrointestinal irritation; therefore, intravenous application is usually preferred [95]. Since mild hypocalcemia can occur due to decreased bone resorption 24–48 h after administration of bisphosphonates, calcium and vitamin D status should be assessed before initiating therapy [96]. Osteonecrosis of the jaw is a serious side effect documented in adult patients treated with bisphosphonates. However, there is no evidence of an increased risk of bisphosphonate-related osteonecrosis in children with OI [97, 98]. The response to bisphosphonates in children with OI is variable and seems to be related to the underlying genetic mutation: Children with structural collagen defects or nonautosomal-dominant inheritance showed less increase of BMD with zoledronic acid therapy [99] and also type VI OI is characterized by a poor response to bisphosphonates [55]. This highlights the limitations of bisphosphonate therapy and the need for tailored therapeutic approaches for certain genetic subtypes.

Anti-RANKL antibodies

Denosumab is a monoclonal antibody administered via subcutaneous injection every 3 to 6 months. It specifically targets and inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL), thereby inhibiting RANKL-induced differentiation of osteoclast precursors to mature bone resorbing cells. Furthermore, denosumab reduces activity and survival time of mature osteoclasts [100–103]. In contrast to bisphosphonates, which remain in the organism for decades [104], denosumab is fully metabolized after a few months [105].

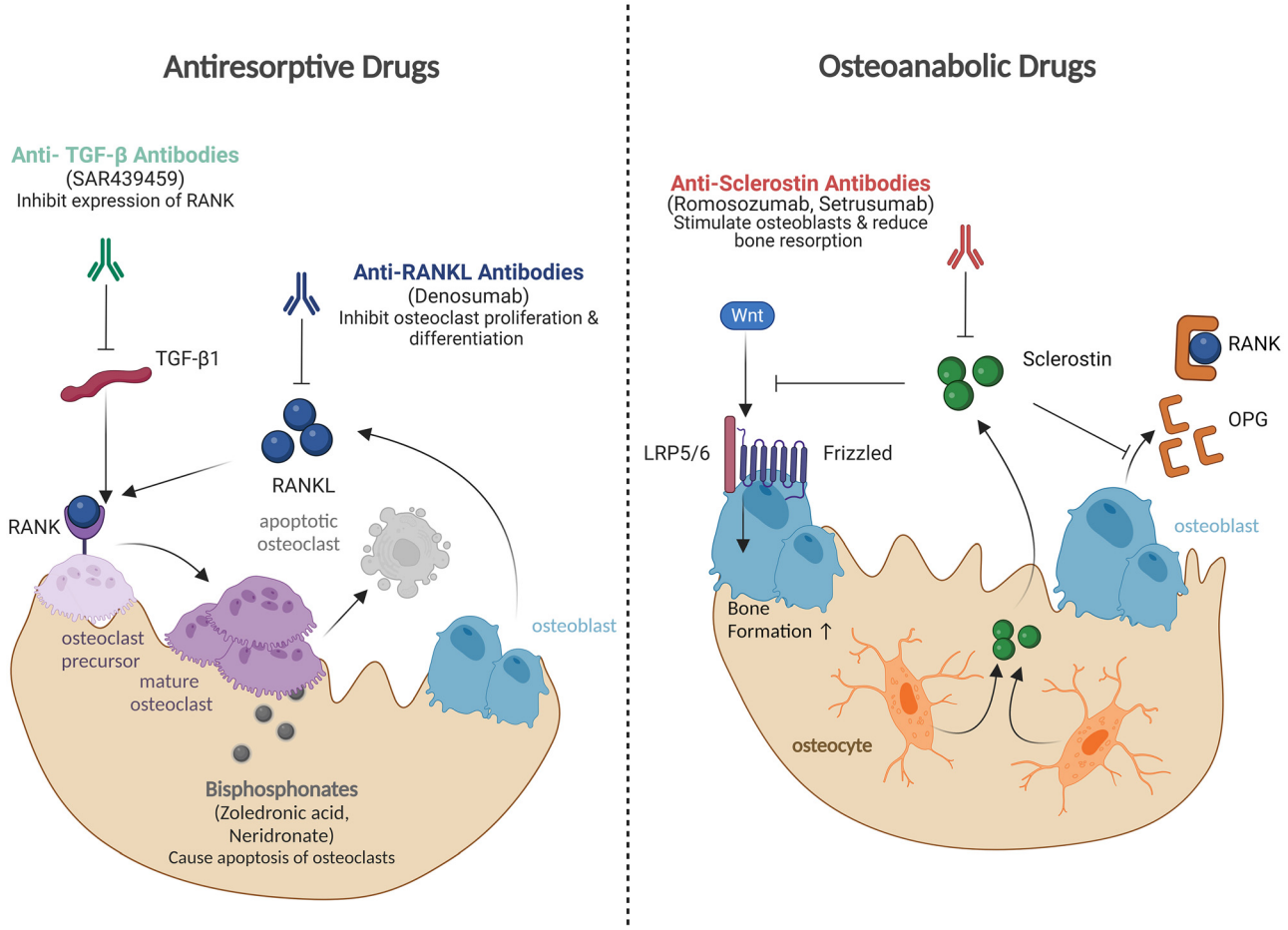

Figure 4: Pharmacological treatment approaches for OI. Most of these approaches are currently being investigated in clinical trials and are not yet approved for OI. Antiresorptive drugs primarily inhibit bone resorption. Denosumab, an anti-RANKL antibody, prevents RANKL-induced osteoclast proliferation and differentiation. Anti-TGF-β antibodies reduce TGF-β-stimulated osteoclastogenesis and expression of RANK on osteoclast precursors. Bisphosphonates (zoledronic acid, neridronate), the current standard of care for OI, induce apoptosis of osteoclasts. Osteoanabolic drugs primarily promote bone formation. Antisclerostin antibodies (romosozumab, setrusumab) inhibit sclerostin, leading to activation of the Wnt signaling pathway and subsequently stimulation of osteoblast activity. Additionally, antisclerostin antibodies exert antiresorptive effects by promoting the secretion of osteoprotegerin (OPG), which inhibits the RANK–RANKL interaction.

Denosumab effectively increased bone mass and areal BMD measured by DXA and reduced fracture incidence in osteoporosis patients [106, 107]. A single-center, 1-year study by Liu et al. (2024) showed previously denosumab to be as effective as the bisphosphonate zoledronic acid in increasing aBMD in children with OI [108]. However, large-scale studies investigating the effects of denosumab in OI are currently lacking due to safety concerns about calcium-related side effects. A pronounced rebound effect 3–7 months after denosumab injections was reported in children and adults [109, 110]. This rebound is associated with excessive bone resorption, leading to a loss of bone mass to pretreatment levels, increased calcium mobilization to the circulation, and an increased risk of fractures [111]. Case reports have described severe hypercalcemia requiring acute hospital admission with hydration and antiresorptive therapy to prevent acute kidney failure [108, 112, 113]. These safety concerns led to the early termination of a large multicenter study that aimed to investigate denosumab in children with OI [114]. Denosumab is, therefore, currently not recommended for the treatment of pediatric OI patients.

Anti-TGF-β antibodies

Excessive TGF-β signaling has been identified in both dominant and recessive forms of OI [115, 116]. Anti-TGF-β treatment using neutralizing antibodies increased bone mass and improved bone architecture in OI mouse models [115] and in adults receiving fresolimumab [117]. A phase 1 clinical study is currently investigating the safety and tolerability of a single dose of SAR439459, another human

anti-TGF-β monoclonal antibody, in adult participants with OI [118].

Osteoanabolic drugs

Recombinant human PTH

Parathyroid hormone (PTH) regulates bone metabolism by stimulating osteoclast activity to increase calcium release into the bloodstream. However, when administered intermittently, PTH stimulates bone formation [119]. In adults with OI, particularly patients with OI type I, teriparatide, a recombinant human PTH, has shown significant increases in BMD compared to placebo and bisphosphonates [120, 121]. However, preclinical studies in rodents receiving high-dose PTH treatment raised concerns about an increased risk of osteosarcoma with long-term use [122]. Therefore, this therapy is not used in children. The TOPaZ trial is currently investigating whether a 2-year treatment with teriparatide followed by a single infusion of zoledronic acid can reduce fracture risk in adult patients with OI compared to standard therapy with zoledronic acid alone [123].

Antisclerostin antibodies

Sclerostin, a glycoprotein predominantly expressed by osteocytes, regulates bone formation by binding to the LRP5/6 receptors on osteoblasts. It inhibits the Wnt/β-catenin signaling pathway, which is essential for osteoblast proliferation, differentiation, and activity. Inhibiting sclerostin reduces β-catenin degradation, thereby enhancing osteoblast activity and bone formation [124, 125]. In murine OI models, treatment with an antisclerostin antibody decreased fracture rates and increased cortical bone thickness and BMD [126, 127]. The effectiveness of the antisclerostin antibody setrusumab was already shown in adult osteoporosis and OI patients [128]. Currently, two antisclerostin antibodies are investigated in phase 3 multicenter studies in pediatric patients with OI to evaluate their effectiveness compared to bisphosphonates: Romosozumab, a monoclonal antibody, which is injected subcutaneously monthly [129], and setrusumab, which is administered monthly via intravenous infusion [130].

Future therapy approaches

Emerging therapies such as mesenchymal stem cell (MSC) therapy and gene therapy offer promising new avenues for treating OI. These approaches aim to address the underlying genetic and cellular defects of the disease, potentially providing long-term or even curative effects.

MSC therapy involves the use of multipotent stromal cells that can differentiate into osteoblasts and chondrocytes. Preclinical studies with animal models have shown that human fetal MSCs can target bone lesions, reduce brittleness, and increase bone thickness and collagen content in OI mice [131]. In humans, bone marrow transplants from siblings have increased growth rates and reduced fractures in children with OI type III [132]. Prenatal MSC transplantation followed by additional postnatal treatments improved growth and fracture reduction in severe OI types III and IV [133]. Challenges include ensuring the effective integration and long-term viability of transplanted MSCs, along with risks such as immune rejection and potential malignant transformation. The BOOSTB4 clinical trial is currently evaluating the long-term safety and efficacy of postnatal vs. prenatal and postnatal administration of fetal MSCs in severe OI [134].

Gene therapy aims to treat OI by directly addressing its genetic defect. Techniques like CRISPR/Cas9 are being explored for precise gene editing in other genetic diseases [135]. However, challenges include developing effective delivery systems and avoiding potential off-target effects.

Summary

OI is one of the most common inherited skeletal disorders. Over the past decades, there has been substantial progress in understanding its genetic background and underlying molecular mechanisms, as well as in improving treatment strategies. Nevertheless, current treatment for OI remains primarily supportive. Future approaches may focus increasingly on personalized, gene-targeted therapies to offer long-term solutions for even the most severe cases. As our understanding of the molecular mechanisms in this disease deepens, we are moving closer to curative therapies that could transform patient care in the future.

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