ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 April 26; 11(12): 2582-2854

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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PUBLICATION DATE
April 26, 2023

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World Journal of Clinical Cases

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World J Clin Cases 2023 April 26; 11(12): 2604-2620

DOI: 10.12998/wjcc.v11.i12.2604

ISSN 2307-8960 (online)

REVIEW

Classification of osteogenesis imperfecta: Importance for prophylaxis and genetic counseling

Monica-Cristina Panzaru, Andreea Florea, Lavinia Caba, Eusebiu Vlad Gorduza

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Muthu S, India; Stogov MV, Russia

Received: January 28, 2023
Peer-review started: January 28, 2023
First decision: March 10, 2023
Revised: March 18, 2023
Accepted: March 27, 2023
Article in press: March 27, 2023
Published online: April 26, 2023

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Abstract

Osteogenesis imperfecta (OI) is a genetically heterogeneous monogenic disease characterized by decreased bone mass, bone fragility, and recurrent fractures. The phenotypic spectrum varies considerably ranging from prenatal fractures with lethal outcomes to mild forms with few fractures and normal stature. The basic mechanism is a collagen-related defect, not only in synthesis but also in folding, processing, bone mineralization, or osteoblast function. In recent years, great progress has been made in identifying new genes and molecular mechanisms underlying OI. In this context, the classification of OI has been revised several times and different types are used. The Sillence classification, based on clinical and radiological characteristics, is currently used as a grading of clinical severity. Based on the metabolic pathway, the functional classification allows identifying regulatory elements and targeting specific therapeutic approaches. Genetic classification has the advantage of identifying the inheritance pattern, an essential element for genetic counseling and prophylaxis. Although genotype-phenotype correlations may sometimes be challenging, genetic diagnosis allows a personalized management strategy, accurate family planning, and pregnancy management decisions including options for mode of delivery, or early antenatal OI treatment. Future research on molecular pathways and pathogenic variants involved could lead to the development of genotype-based therapeutic approaches. This narrative review summarizes our current understanding of genes, molecular mechanisms involved in OI, classifications, and their utility in prophylaxis.

Key Words: Osteogenesis imperfecta; Heterogeneity; Classification; Molecular mechanism; Genetic counseling; Prophylaxis

Core Tip: Osteogenesis imperfecta (OI) is a genetically heterogeneous systemic collagenous disorder with high phenotypic variability. Recent discoveries of new genes and molecular mechanisms underlying the disease have led to revisions of classical classification. Identifying the causative gene and molecular mechanisms allows a personalized management strategy, accurate family planning, and pregnancy management decisions including options for mode of delivery, or early antenatal OI treatment.

Citation: Panzaru MC, Florea A, Caba L, Gorduza EV. Classification of osteogenesis imperfecta: Importance for prophylaxis and genetic counseling. *World J Clin Cases* 2023; 11(12): 2604-2620
URL: https://www.wjgnet.com/2307-8960/full/v11/i12/2604.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i12.2604

INTRODUCTION

Osteogenesis imperfecta (OI) is a rare monogenic disorder with an incidence estimated at about 1 per 10000 individuals[1]. It is a genetically and clinically heterogeneous disease characterized by decreased bone mass and bone fragility. This generates susceptibility to fractures with minimal or no trauma, vertebral compressions, variable skeletal deformities, and growth deficiency. Bone tissue is characterized by alterations of trabecular architecture, thin cortex, high bone turnover, and hypermineralized matrix. Patients with OI have a broad phenotypic spectrum ranging from prenatal fractures and pre and perinatal lethal outcome to mild forms with few fractures and normal stature. This phenotypic variability is only partially explained by the type of mutation or causative gene. Patients with the same pathogenic variant may present variable degrees of phenotype expression. The basic mechanism is a collagen-related defect, not only in structure or production, but also in folding, posttranslational processing, bone mineralization or osteoblast differentiation[2]. The disorder is a systemic collagen disorder and it also has extra-skeletal manifestations like blue-gray sclera, dentinogenesis imperfecta, conductive or sensory hearing loss, ligamentous laxity, muscle weakness, respiratory impairment, increased fragility of vessels, and cardiac valve abnormalities[1,3-5].

COLLAGEN SYNTHESIS

Collagen is a major component of the extracellular matrix, with essential roles in mechanical resistance and regulation of several signaling pathways. Type I collagen is a crucial skin, bone, tendons, lungs, heart, and blood vessels constituent. This collagen is a heterotrimer synthesized in a precursor form, procollagen, containing two proα1(I) and one proα2(I) chains. The procollagen has a rod-like central triple-helical domain with globular extensions at the N- and C- ends. The helical core contains repeating Gly-Xaa-Yaa tripeptides, where X is often proline and Y hydroxyproline. Type I procollagen synthesis is a complex process, involving numerous phases and many proteins necessary for post-translational modifications, folding, transport, and secretion. The proα1(I) and proα2(I) polypeptide chains, encoded by the *COL1A1* and *COL1A2* genes, are translated in the rough endoplasmic reticulum (ER). The post-translational modifications include 4hydroxylation of most prolines in the Yaa position – essential for triple helical stability. The complex formed by P3H1 – CRTAP – PPIB and the FKBP10 protein have an important role in triple helix formation. Serpin H1 is involved in the stabilization of the triple helix and transport to the Golgi apparatus. The terminal procollagen extensions are cleaved by specific proteases: Disintegrin, metalloproteinase with thrombospondin motifs 2 (ADAMTS2) and bone morphogenetic protein 1 (BMP1). Three specific regions, relevant to the interaction of collagen with other collagen molecules or extracellular matrix proteins, were identified along the α1chain - major ligand-binding regions (MLBRs), which are very important for matrix quality[6-9]. Pathogenic variants in gene-encoding key players in these processes lead to collagen defects and OI phenotype.

CLASSIFICATION

Lately, OI classification has been the subject of extensive debates and has been revised several times. In 1979, Sillence proposed a classification based on clinical/radiological characteristics and mode of inheritance: OI type I - autosomal dominant (AD) with blue sclerae, OI type II - perinatal lethal form with radiographically broad, crumpled femora and beaded ribs, OI type III - progressively deforming,

and OI type IV – dominant with normal sclerae[10] (Figure 1). This classification included only patients with defects in the primary structure of collagen. The discovery of pathogenic variants in new genes with clinical overlap with previous types has caused many debates. In 2014, Van Dijk and Sillence suggested the addition of OI type V – a form with calcification in the intraosseous membranes[11]. The revised nosology and classification of genetic skeletal disorders recognizes these five clinical types (but Arabic numerals are used), with subclasses based on inheritance patterns and genes involved[12]. Some types (*e.g.* 3 or 4) have many genes and different inheritance (dominant/ recessive) resulting in challenges for genetic counseling. An alternative functional classification based on the metabolic mechanism was also proposed: Group A - defects in collagen synthesis, structure, or processing, group B - defects in collagen modification, group C - collagen folding and cross-linking defects, group D - compromised bone mineralization, and group E - defects in osteoblast development with collagen insufficiency[8,13]. The Online Mendelian Inheritance in Man database uses a mixed-genetic classification, with types I–IV according to the Sillence classification and pathogenic variants in *COL1A1* or *COL1A2*, and the new gene-classified type[1] (Table 1). The advantages of genetic classification are the identification of the inheritance pattern for counseling, prophylaxis, and the possibility of grouping for etiology-based therapies research.

GENES AND PROTEINS INVOLVED IN OI

COL1A1 and COL1A2

Over 85% of OI cases are associated with pathogenic variants in *COL1A1* and *COL1A2* genes, which lead to quantitative or qualitative alterations of collagen. These mutations generate OI types I - IV. Pathogenic variants (mostly nonsense mutations) lead to haploinsufficiency and reduce the amount of normal collagen, thus generating a milder phenotype. In contrast, pathogenic variants leading to structural collagen defects cause a more severe phenotype. The most common mutations are single-nucleotide variants resulting in the substitution of a glycine residue. Substitutions in gene regions that encode branched-chain or charged amino acids interfere with triple helix folding and are associated with severe clinical consequences. Substitutions on the α1(I) chain have a more severe/Lethal outcome than those in α2(I). The nature of the substituting amino acid, the chain in which it is located, and its position along the chain influence the phenotype. Pathogenic variants in the 3' or 5' splice sites that produce exon skipping do not affect the Gly-Xaa-Yaa triplet pattern but may cause local looping out of chains[1,2]. Pathogenic variants in the C-terminal propeptide, which is cleaved from the mature collagen, impair chain association or delay the incorporation into the collagen trimer[14]. Deletions or duplications of the codons for one or two Gly-Xaa-Yaa triplets shift the chain alignment without interrupting the sequence and produce severe or lethal phenotypes[15]. Due to the direction of the zipper-like folding of the chains, pathogenic variants in the N-terminal region have minimal consequences, whereas those in the C-terminal region cause moderate to lethal outcomes. Substitutions in MLBR3 regions impair extracellular matrix organization and usually have lethal consequences. In the α2(I) chain, severe pathogenic variants are gathered in clusters that are correlated with the proteoglycan binding site on collagen fibrils[16-19] .

IFITM5

Interferon-induced transmembrane protein 5 (IFITM5), also known as bone-restricted IFITM-like, is a short transmembrane protein expressed specifically in osteoblasts and attached to the cell membrane by palmitoylation of cysteines 50 and 5, with a regulatory role in mineralization. IFITM5 plays a crucial role in the regulation of *SERPINF1* expression and the resultant production of the protein pigment epithelium-derived factor (PEDF). Different pathogenic variants in *IFITM5* gene lead to a distinct OI phenotype, named OI V. A heterozygous gain of (new) function variant in the 5' untranslated region (c.-14C>T) is associated with a moderate type of OI with distinctive radiographic findings. This pathogenic variant creates a new start codon, resulting in the elongation of the cytoplasmic N- terminus of IFITM5 protein by five amino acids and inducing increased bone formation[2,20,21]. The characteristic radiographic findings include hyperplastic callus formation, calcification of the interosseous membrane of the forearm, and hyperdense metaphyseal band. Some patients may present radial head dislocation. Histologic examination of bone under polarized light reveals a "*mesh-like pattern*" of irregularly arranged lamellar deposition[22]. Heterozygous missense variants lead to substitution of the serine at position 40 (c.119C>T and c.119C>G), impairment of the palmitoylation process, and are associated with a more severe phenotype. Patients present prenatal fractures or shortening/ bowing of long bones, a severe deforming course, and a fish-scale lamellar pattern at the bone examination under polarized light. Patients do not show radial head dislocation or signs from the radiographic triad. Lim *et al*[23] reported a case of gonadal mosaicism in the unaffected mother[24]. Bisphosphonates (BPs) are more effective in patients with c.119C>T variant than in cases with other variants[25].

Table 1 Genes and proteins in osteogenesis imperfecta[1,2,8,13,17-19]

OI type	OMIM	Gene symbol	Approved gene name	Location	Protein name	Functional group
I	166200	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
II	166210	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
		COL1A2	Collagen type I alpha 2 chain	7q21.3	Collagen alpha-2(I) chain	
III	259420	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
		COL1A2	Collagen type I alpha 2 chain	7q21.3	Collagen alpha-2(I) chain	
IV	166220	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
		COL1A2	Collagen type I alpha 2 chain	7q21.3	Collagen alpha-2(I) chain	
V	610967	*IFITM5*	Interferon induced transmembrane protein 5	11p15.5	Interferon-induced transmembrane protein 5	D
VI	613982	*SERPINF1*	Serpin family F member 1	17p13.3	Pigment epithelium-derived factor	D
VII	610682	*CRTAP*	Cartilage associated protein	3p22.3	Cartilage-associated protein	B
VIII	610915	*P3H1*	Prolyl 3-hydroxylase 1	1p34.2	Prolyl 3-hydroxylase 1	B
IX	259440	*PPIB*	Peptidylprolyl isomerase B	15q22.31	Peptidyl-prolyl cis-trans isomerase B	B
X	613848	*SERPINH1*	Serpin family H member 1	11q13.5	Serpin H1	C
XI	610968	*FKBP10*	FKBP prolyl isomerase 10	17q21.2	Peptidyl-prolyl cis-trans isomerase *FKBP10*	C
XII	613849	*SP7*	Sp7 transcription factor	12q13.13	Transcription factor Sp7	E
XIII	614856	*BMP1*	Bone morphogenetic protein 1	8p21.3	Bone morphogenetic protein 1	A
XIV	615066	*TMEM38B*	Transmembrane protein 38B	9q31.2	Trimeric intracellular cation channel type B	B
XV	615220	*WNT1*	Wnt family member 1	12q13.12	Proto-oncogene Wnt-1	E
XVI	616229	*CREB3L1*	cAMP responsive element binding protein 3 like 1	11p11.2	Cyclic AMP-responsive element-binding protein 3-like protein 1	E
XVII	616507	*SPARC*	Secreted protein acidic and cysteine rich	5q33.1	*SPARC*	E
XVIII	617952	*TENT5A*	Terminal nucleotidyltransferase 5A	6q14.1	Terminal nucleotidyltransferase 5A	Unclassified
XIX	301014	*MBTPS2*	Membrane bound transcription factor peptidase, site 2	Xp22.12	Membrane-bound transcription factor site-2 protease	E
XX	618644	*MESD*	Mesoderm development LRP chaperone	15q25.1	LRP chaperone MESD	Unclassified
XXI	619131	*KDELR2*	KDEL ER protein retention receptor 2	7p22.1	ER lumen protein-retaining receptor 2	C
XXII	619795	*CCDC134*	Coiled-coil domain containing 134	22q13.2	Coiled-coil domain-containing protein 134	Unclassified

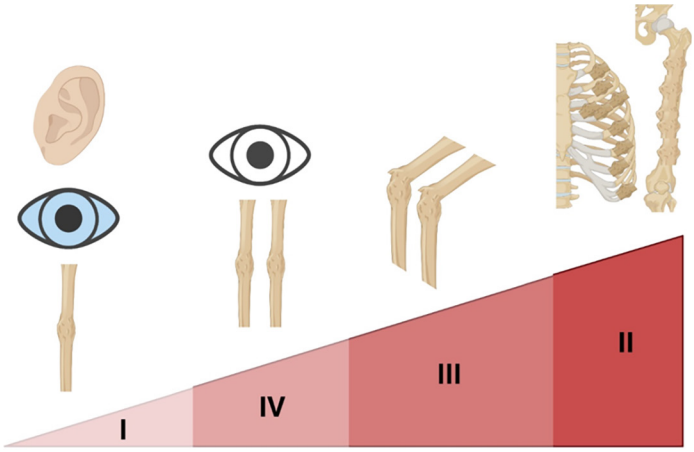
OI: Osteogenesis imperfecta; OMIM: Online Mendelian Inheritance in Man; ER: Endoplasmic reticulum; LRP: Lipoprotein receptor-related protein.

SERPINF1

PEDF, encoded by *SERPINF1* gene, is a ubiquitously expressed protein, with anti-angiogenic, anti-tumorigenic, and anti-metastatic properties. The binding of PEDF to type I collagen is essential for anti-angiogenic properties. PEDF induces the expression of osteoprotegerin which interacts with the receptor activator of nuclear factor-κβ ligand (RANKL) pathway and regulates the activity of osteoclasts. Kang *et al*[26] suggest that antagonism between PEDF and TGF-β pathways controls osteogenesis and bone vascularization[8,27]. Patients with biallelic pathogenic variants in *SERPINF1* have postnatal fractures, progressive skeletal deformity, vertebral compressions, and a fish-scale pattern at bone examination under polarized light (similar to patients with loss of function mutation in *IFITM5*). These mutations produce OI type VI. The RANKL-antibody is a potential therapeutic agent for this form of OI[1,4,28].

CRTAP, P3H1 and PPIB

Cartilage-associated protein (CRTAP) forms a complex with prolyl-3-hydroxylase 1 (P3H1) and peptidyl-prolyl-cis-transisomerase B (PPIB). This complex is involved in 3-hydroxylation of specific proline residues. Chang *et al*[29] showed that CRTAP and P3H1 are mutually stabilized in the collagen prolyl 3-hydroxylation complex. Biallelic pathogenic variants in *CRTAP* or *P3H1* genes lead to a marked decrease in proline hydroxylation and subsequently to a delay in collagen folding and are associated



DOI: 10.12998/wjcc.v11.i12.2604

Figure 1 Clinical osteogenesis imperfecta classification (severity). OI type I – mild form with blue sclerae, hearing loss; OI type IV – mild to moderate form with normal sclerae; OI type III - progressively deforming; OI type II – extremely severe form, lethal perinatal outcome with radiographically broad, crumpled femora and beaded ribs (Created with BioRender.com). OI: Osteogenesis imperfecta.

with a severe/lethal form of OI. Patients have neonatal fractures, rhizomelia, and undertubulation of the long bones[4,13,30-31]. Biallelic pathogenic variants in *PPIB* gene are associated with a low percentage of 3-hydroxylated proline at position 986, but higher than in *CRTAP* or *P3H1* genes mutations. The phenotype overlaps with that caused by *CRTAP* or *P3H1* genes mutation, with the exception of rhizomelia[32,33]. *CRTAP* genes mutations determine OI type VII, *P3H1* genes mutations determine OI type VIII, while *PPIB* genes mutations determine OI type IX.

SERPINH1

Serpin H1 is a collagen-specific chaperone, that localizes in the ER and is encoded by *SERPINH1* gene. Serpin H1 binds to arginine-rich sequences of triple helical collagen and stabilizes it by preventing unfolding and aggregate formation. Also, serpin H1 participates in the shuttling of correctly folded collagen into the Golgi apparatus. Homozygous or compound heterozygous pathogenic variants in *SERPINH1* gene lead to misfolding, intracellular aggregation, and delayed collagen secretion and are associated with a moderate to severe form of OI – OI type X[34-36].

FKBP10

Serpin H1 interacts with peptidyl-prolyl cis-trans isomerase FKBP10, another collagen chaperone, which provides mutual stability and allows for a synergistic effect during collagen folding. FKBP10 is also required for the activity of lysyl hydroxylase 2 (LH2, encoded by *PLOD2* gene). Hydroxylation of the collagen telopeptide lysyl residues is essential in cross-linking. Recessive pathogenic variants in *FKBP10* gene are associated with a wide clinical spectrum which includes a progressive deforming form of OI (OI type XI), Bruck syndrome, and Kuskokwim syndrome. Bruck syndrome is characterized by congenital contractures with pterygia, early onset of fractures, short stature, limb deformity, and progressive scoliosis. Bruck syndrome 2 presents a similar phenotype, but it is generated by a biallelic pathogenic variant in *PLOD2* gene. Kuskokwim syndrome is a congenital contracture disorder with mild skeletal anomalies, occurring in Yup'ik Eskimos in Alaska. Bisphosphonate therapy reduces the fracture rate and pain but has no effect on joint abnormalities[4,37-39].

SP7

SP7 gene encodes transcription factor SP7, a key regulator of osteoblast differentiation and subsequently of osteocyte formation. Recessive pathogenic variants in *SP7* are associated with increased bone porosity, recurrent fractures, skeletal deformities, delayed teeth eruption and hearing loss. This particular phenotype is characteristic to OI type XII. Recently, heterozygous (dominant) missense variants affecting a highly conserved zinc finger domain have been reported in cases with bone fragility, high bone turnover, and patchy sclerosis[40-43].

BMP1

The major function of bone morphogenetic protein 1 (BMP1) involves procollagen I C-terminal propeptide processing, crucial for fibril formation. Other roles are activation of lysyl oxidases (involved in cross-linking), processing of small leucine-rich proteoglycans (*e.g.* decorin - important for collagen fibrillogenesis) and dentin matrix protein 1 involved in bone mineralization, and activation of TGFβ1, a key signaling molecule for bone remodeling. Patients with homozygous or compound heterozygous pathogenic variants in *BMP1* gene present a variable phenotype ranging from mild to severe

progressive deforming OI (OI type XIII). Individuals with *BMP1* pathogenic variants with residual activity of the protein have a milder phenotype than cases with null pathogenic variants. In the majority of cases, increased bone mineral density (BMD) has been noticed. In this context, the indication, dose, and duration of antiresorptive therapy are questionable due to concerns about increasing bone stiffness leading to fracture[2,44-47].

TMEM38B

TMEM38B gene encodes TRimeric Intracellular Cation channel type B (TRIC-B), specific for potassium, also known as transmembrane protein 38 (TMEM 38B). TMEM 38B is involved in the opening of cation channels, after calcium release, and thus the ER membrane potential is maintained. Disruption of intracellular calcium kinetics affects the activity of many proteins required for type I collagen synthesis and folding[48,49]. Webb *et al*[50] revealed characteristics of bone modifications in patients with biallelic *TMEM38B* pathogenic variants: Decreased hydroxylation of collagen helical lysine residues and intracellular retention and degradation of misfolded collagen. The phenotypic spectrum varies considerably ranging from mild scoliosis to severe cases with prenatal bowed femur, early-onset multiple fractures, and growth retardation (OI type XIV). The variability in phenotype severity indicates that other factors may be involved, including genetic modifiers, different genetic backgrounds, and other genes involved in intracellular calcium dynamics. Patients responded well to BPs, but, in some cases, cardiovascular abnormalities and hypotonia were reported (possibly related to abnormal ER calcium kinetics)[51-54].

WNT1

Proto-oncogene Wnt-1 (the wingless-type mouse mammary tumor virus integration site family, member 1) is a glycoprotein with a key role in bone development. WNT1 interacts with the cell surface lipoprotein receptor-related protein 5 (LRP5) and Frizzled receptor leading to the translocation and accumulation of beta-catenin into the cell nucleus and subsequent transcriptional regulation of target genes. WNT/β-catenin signaling is involved in osteoblast progenitor proliferation, osteoblast differentiation, and regulation of osteoclastogenesis in mature osteoblasts and osteocytes through the secretion of osteoprotegerin[55-57]. The WNT/β-catenin pathway is an activator of *BMP2* gene transcription, a member of the TGF-β gene superfamily essential for osteoblast differentiation and osteogenesis[57]. Biallelic pathogenic variants in *WNT1* gene lead to moderate-severe OI, whereas heterozygous *WNT1* gene mutations are reported in patients with 'early-onset osteoporosis' indicating a gene dose effect. Neurologic features such as hypotonia, ptosis, developmental delays, and brain anomalies have been reported in some patients with OI type XV[57-60].

CREB3L1

Cyclic AMP-responsive element-binding protein 3-like protein 1 (CREB3L1), also known as old astrocyte specifically induced substance (OASIS), a leucine zipper transcription factor is encoded by *CREB3L1* gene. In osteoblasts, CREB3L1 is activated by regulated intramembrane proteolysis (RIP) and induces the transcription of *COL1A1* gene by binding to the UPR element-like sequence in its promoter. Also, CREB3L1 plays an important role in the expression of coat protein complex II component SEC24D, involved in procollagen export from ER[45,61,62]. Phenotype severity varies considerably ranging from forms with prenatal fractures, severe demineralization, and early lethal outcome to cases with severe bone deformities and survival to adulthood (OI type XVI). Severe phenotypes are caused by homozygous whole gene deletions or in frame deletions in a highly conserved DNA binding domain (loss of function). Siblings with heterozygous pathogenic variants are mildly affected: fractures with minimal trauma, blue sclerae, and osteopenia[61,63]. Truncating homozygous pathogenic variants (outside the highly conserved DNA binding domain) led to a non-lethal phenotype, while heterozygotes are unaffected[64,65].

SPARC

Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or basement membrane protein 40, has a collagen-binding domain and a hydroxyapatite (necessary for mineralization of the collagenous matrix) binding site. During bone development, SPARC is secreted by osteoblasts and has important roles in procollagen processing and assembly in the bone matrix, cross linking, and mineralization[66,67]. Pathogenic variants (substitution, nonsense or splice site) that affect the collagen-binding domain have been reported in patients with OI. Common features of this type of OI (OI type XVII) are multiple postnatal fractures, scoliosis, delayed motor development, neuromuscular weakness (especially of the lower extremities), and brain MRI abnormalities[68-70].

TENT5A

Terminal nucleotidyltransferase 5A (TENT5A) belongs to the nucleotidyltransferase fold superfamily proteins and acts as a noncanonical poly(A) polymerase. TENT5A forms a complex with SMAD proteins and induces transcription of BMP target genes. TENT5A is involved in embryonic development, adult bone formation, and hemin-induced hemoglobinization[2,71,72]. Doyard *et al*[73] reported biallelic

pathogenic variants (nonsense or missense) in *TENT5A* genes in patients with a severe form of OI (OI type XVIII) with multiple fractures, severe bowing of lower limbs, joint hyperlaxity, vertebral collapses, and blue sclerae. Lin *et al*[71] considered TENT5A a molecular modulator and a future therapeutic target.

MBTPS2

An X-linked form of OI (OI type XIX) is caused by a mutation in *MBTPS2*, a gene that encodes the membrane-bound transcription factor protease, site-2 (MBTPS2), also known as site-2 protease, a component of the RIP pathway. ER stress - due to retention of unfolded proteins - leads to translocation of CREB3L1, sterol regulatory element-binding protein, and activating transcription factor 6, from the ER membrane to the Golgi membrane, where they are cleaved by endoproteases MBTPS1 and MBTPS2. The resulting fragments regulate the production of collagen and matrix components in the nucleus[1,2,74]. Substitutions that affect a highly conserved MBTPS2 motif, essential for zinc ion coordinating site, are associated with reduced hydroxylation of lysine 87 in both α collagen chains and altered collagen cross-linking. Patients have a form of moderate-to-severe OI with prenatal fractures, generalized osteopenia, long bone bowing, short stature, pectus deformity, and scoliosis, but no dermatological features[75]. Missense pathogenic variants elsewhere in *MBTPS2* have been associated with dermatological conditions - IFAP (ichthyosis follicularis, atrichia, and photophobia) syndrome with or without BRESHECK (Brain anomalies, severe mental Retardation, Ectodermal dysplasia, Skeletal deformities, Ear/eye and Kidney dysplasia/hypoplasia) syndrome, Olmsted syndrome (mutilating palmoplantar keratoderma with periorificial keratotic plaques), and keratosis follicularis spinulosa decalvans[76-78].

MESD

MESD gene (mesoderm development) encodes an ER chaperone for the WNT signaling receptors LRP5 and LRP6. Moosa *et al*[79] reported patients with biallelic pathogenic variants (frameshift predicted to result in a premature termination codon or substitution that removes a highly conserved domain) in exon 3 of *MESD* gene, with partial loss of function, and a progressively deforming type of OI with oligodontia and developmental delay. BPs were not effective in these patients, but antisclerostin antibodies that affect Wnt signaling could be a valid therapeutic option. Two infant deaths due to respiratory insufficiency were reported. Stürznickel *et al*[80] reported three stillbirths with multiple intrauterine fractures and compound heterozygous frameshift pathogenic variants in exon 2 and exon 3 of *MESD* gene. They blamed the lethal phenotype on a complete loss of function mutation, located within the chaperone domain of MESD (exon 2)[80].

KDELR2

KDELR2 gene encodes ER lumen protein-retaining receptor 2, involved in protein with a KDEL-like peptide traffic from the Golgi to the ER. The protein binds heat shock protein 47 (HSP47), with an essential role in the intracellular processing of procollagen. Biallelic pathogenic variants in *KDELR2* gene are associated with abnormal collagen fibril formation due to the failure of HSP47 to dissociate from collagen type 1. Patients present a progressively deforming type of OI. Efthymiou *et al*[81] reported neurodevelopmental disorders (motor and speech delay) in three cases[82].

CCDC134

CCDC134 gene encodes a secreted coiled-coil domain-containing protein, involved in the regulation of MAPK pathway, especially phosphorylation of the extracellular signal-related kinase (Erk) or c-JUN N-terminal kinase (JUNK). Erk1/2 and JUNK have an important role in bone morphogenesis, by regulating osteoblast extracellular matrix protein deposition in response to stress. Loss of function pathogenic variants in *CCDC134* gene were associated with reduced *COL1A1* and *SPP1* (ostepontin) mRNA expression and mineralization in osteoblasts. Dubail *et al*[83] reported patients with homozygous pathogenic variants in *CCDC134* gene and a severe form of OI with intrauterine growth retardation, multiple pre and postnatal fractures, short stature, low mineral density, and no response to BPs[84,85].

GENETIC COUNSELING AND PROPHYLAXIS

The identification of the inheritance pattern is essential for genetic counseling and management. Up to 90% of OI patients have an AD pathogenic variant in *COL1A1, COL1A2,* or *IFITM5* genes, with a 50% risk to transmit this variant to their offspring[86]. Nearly half of the OI cases are caused by *de novo* pathogenic variants[87]. Although advanced paternal age is associated with a high risk of *de novo* pathogenic variants in monogenic disorders, Mei *et al*[88] reported a significantly younger paternal and maternal age at conception in OI patients with a *de novo* mutation. Pyott *et al*[89] reported a 16% rate of parental mosaicism in couples with a child affected by lethal AD OI. In couples with two or more children with lethal AD OI, the recurrence rate of this mosaicism was 27%[89]. The rate of parental mosaicism is estimated at approximately 5–8% in all OI cases[86]. Persons with mosaicism for AD

pathogenic variants are often asymptomatic or have subtle clinical findings depending on the percentage of cells that carry the pathogenic variant[88].

About 10% of OI patients have pathogenic variants with autosomal recessive (AR) inheritance. The distribution of these AR variants is different across populations due to consanguinity or founder effect. In a genetically isolated Dutch group, the carrier frequency of a *CRTAP* frameshift variant was 4.1% while in the general Dutch population is < 0.2%[90]. Founder pathogenic variants in other genes associated with recessive OI have been reported: *P3H1* in West African, United States African American populations and ethnic Kinhs, *TMEM38B* in Palestinians, and Israeli Arab Bedouins, *FKBP10* in indigenous southern Africans, Palestinians, Bavarians, and Samoan islanders, *SEC24D* in southwestern Germans, *WNT1* in the Finnish Hmong group, and *PPIB* in Chinese people[33,91-95]. A few cases with X-linked pathogenic variants in *MBTPS2* or *PLS3* have also been reported[75,96].

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 phenotypical variability, in association with genetic or epigenetic modifiers[97]. Some OI lethality/ severity prediction algorithms were established with variable accuracy[98].

Preconception carrier screening is recommended in healthy couples in different circumstances: positive OI family history, consanguineous marriage, or members of founder populations. Carrier screening cannot detect parental germline mosaicism or predict the possibility of *de novo* pathogenic variants. A couple with a significant recurrence risk - affected parent(s), carriers of AR pathogenic variants - has many reproductive options: *In vitro* fertilization (IVF) with gamete or embryo donation, IVF with own cells, and preimplantation genetic diagnosis (PGD), adoption, or natural pregnancy with prenatal diagnosis. Gamete donation is usually recommended in couples with infertility or affected women, because repeated superovulation procedures are associated with an increased risk of osteoporosis and cardiovascular problems[99]. PGD has the advantage of also detecting aneuploidies, but the accuracy rate is 95 to 99.5%, so there is a small risk of false negative results. Moreover, the success rate for artificial reproductive techniques is below 30%. Prenatal testing should be recommended after implantation to confirm the PGD result. In this context, a debatable issue is the transfer of AR variants heterozygous embryos. A parental argument not to transfer an AR carrier embryo would be the prevention of difficult reproductive options for the future child[86,100,101].

Prenatal testing

Prenatal genetic testing includes non-invasive prenatal testing (NIPT), and invasive techniques. NIPT has the advantages of early testing (first trimester), less invasive procedure (circulating cell-free fetal DNA extracted from maternal blood), and no associated miscarriage risk. The disadvantages of NIPT are the risk of false-positive, false-negative, or inconclusive results due to confined placental mosaicism (the trophoblastic origin of cell-free fetal DNA is associated with a much higher mutation rate than other fetus cells), or vanishing twin syndrome. NIPT is technically challenging for X-linked and for AR forms when both parents are carriers of the same pathogenic variant due to the presence of the relevant variant from maternal cells in the circulating cell-free DNA. Moreover, NIPT does not cover all the genes involved in OI pathogeny. NIPT results should be confirmed by invasive prenatal testing[102-106].

Invasive prenatal testing uses fetal cells extracted by chorionic villus sampling (CVS), amniocentesis, or cordocentesis, and is associated with an increased risk of pregnancy complications, including fetal loss. CVS has an associated risk of false results due to confined placental mosaicism but allows biochemical type I collagen analysis in extracted cells. Amniocentesis avoids misdiagnosis due to placental mosaicism or twin pregnancy but is performed in the second trimester, after 15 wk of pregnancy, and thus means a long distressful waiting period for the couple. Prenatal diagnosis allows pregnancy management decisions, including the alternative to terminate pregnancy or options for mode of delivery, early OI treatment, before (mesenchymal stem cell transplantation), or after birth[86,107,108].

Ultrasound screening

Severe and lethal forms of OI could be detected by ultrasound screening in the second trimester. Abnormal ultrasound findings suggestive of severe OI include long bone shortening (especially femur length), bowing, and multiple fractures. Moreover, lethal forms have severe demineralization with a thin, easily compressible calvarium, and no posterior acoustic shadowing from long bones[107,109]. Femur length-to-abdominal circumference ratio < 0.16, fetal lung volume below the fifth percentile for gestational age (measured by ultrasound or MRI), and polyhydramnios were associated with lethal outcome. Ultrasound findings do not allow an accurate differential diagnosis with other skeletal dysplasias[107,110,111]. Three-dimensional helical computed tomography provides more accurate data about skeletal anomalies but there are concerns regarding the safety of radiation exposure (even to low

doses)[112].

Mode of delivery

In the past, cesarean delivery was considered safer and more useful for the prevention of fractures at birth than vaginal delivery. Recent studies on babies with types I, III and IV of OI showed that the delivery mode does not influence the rate of fractures at birth. Also, the breech presentation seems to be more frequent in OI type III. Bellur *et al* suggested that cesarean delivery should be performed only for usual maternal or fetal indications, not for fracture prevention in OI. Pregnant women affected by OI require close monitoring to detect possible complications such as cardiorespiratory problems, bone loss, cephalopelvic disproportion, uterine and placenta rupture, and excessive bleeding at delivery[107,113-115].

Therapy

The OI treatment includes physical therapy, medication, and surgical procedures. The major goals are the prevention of fractures, and deformities, maximizing the patient's functional ability, and reducing pain. Fracture healing might be delayed in cases with pathogenic *WNT1* gene variants, or might be altered by hyperplastic callus formation in patients with pathogenic *IFITM5* gene variants. Surgical procedures are used for complex fractures or when correction of deformities is necessary. Intramedullary telescopic rods are used during growth because these have the ability to lengthen. OI patients have anesthetic risks due to abnormal shape or airway, impaired lung function, or the possibility of cervical spine fracture during intubation[4,116]. The rate of fractures decreases in adulthood but the risk of joint osteoarthritis increases[13]. Physiotherapy is essential to improve mobility, due to hypotonia and ligament laxity. Obstructive pulmonary disease (type I collagen is present in lung parenchyma) and scoliosis lead to respiratory complications, a major cause of mortality in OI[117]. Cardiovascular complications include aortic root dilatation left valvular regurgitation, and aortic root dilatation with dissection risk[118]. A multi-disciplinary approach is recommended to address problems related to bone fragility, and also extra-skeletal manifestations.

Antiresorptive bone therapy

BPs are currently the most commonly used pharmacological agents in the treatment of pediatric OI. BPs bind to the hydroxyapatite crystals, promote osteoclasts apoptosis, and decrease bone resorption and remodeling. BPs also interact with osteocytes and interfere with osteoblast recruitment on eroded surfaces[119]. Intravenous infusion is superior to oral administration in improving BMD and decreasing fracture rate. Studies reported that maximum benefits are obtained after 3 years of treatment, but there is no difference in adult fracture rates[120-123]. Long-term treatment is associated with microcrack accumulation and increased potential of progression into fractures, loss of microstructural integrity, and reduced mechanical strength[124]. Another disadvantage of BPs is their long half-life; BPs persist in the bone for years after drug discontinuation. Green *et al*[125] reported decreased birth weight and transient neonatal electrolyte abnormalities (hypocalcemia, hypercalcemia, hyperphosphatemia) associated with maternal use of BPs before or during pregnancy. Whether BPs should be used for a long time at similar or lower doses is debatable. Also, BPs do not have the same efficiency in all types of OI[13,126].

Denosumab is a monoclonal antibody that targets RANKL and inhibits osteoclast activity without binding to the bone. The mechanism of action is similar to BPs, antiresorptive. Denosumab has a shorter half-life (months) and showed promising results in increasing BMD in a few studies. Further studies are necessary to assess the efficiency of fracture prevention[126,127].

Osteo-anabolic agents

Osteo-anabolic therapies stimulate osteoblast activity and bone formation, instead of inhibiting osteoclast function as antiresorptive. Growth hormone (GH) has been used to stimulate long bone growth in GH deficiency, but GH therapy showed only limited benefits in increasing bone mass density compared to BPs (mostly in OI type IV). GH has been less efficient in the more severe forms of OI (type III)[128,129]. Teriparatide, a recombinant parathyroid hormone, leads to a significant increase in BMD in adults with type I OI but seems less effective in patients with types III and IV. Teriparatide has not been used for more than 24 mo and its use in children is contraindicated due to the concern of increased risk of osteosarcoma reported by animal studies[116,129-131]. Lately, the US FDA removed the warning because the risk was only confined to animal studies.

Sclerostin-inhibitory antibodies, romosozumab, and setrusumab, neutralize sclerostin, a negative regulator of Wnt signaling in osteoblasts. Studies revealed good responses of BMD and bone turnover markers to sclerostin-inhibitory antibody treatment in adults with OI[132,133]. Lv *et al*[134] revealed that romosozumab might increase the risk of cardiovascular adverse events in the elderly.

Animal studies have shown that TGF-β signaling is an essential element of pathogenesis, and blocking TGF-β improves bone mass and biomechanical properties, so anti-TGF-antibodies could represent a valuable therapeutic option. Song *et al*[135] reported an increase of BMD in children with type IV OI treated with fresolimumab (an anti-TGF-antibody), but no effect in type III and VIII OI. Losartan, an angiotensin II receptor blocker may also have anti-TGF properties[135]. Losartan increased

bone mass and accelerated chondrocyte hypertrophy in the growth plate in an animal study[136].

Cell therapy and gene editing

Stem cell therapy is a promising pre and postnatal option based on the cells' ability to differentiate into osteoblasts that produce normal collagen. Transplantation of bone marrow from HLA-matched siblings and prenatal and postnatal transplantation of mesenchymal stem cells have been associated with improved growth and reduction of fractures rate. In the first group (bone marrow from HLA-matched siblings), the effect was transient, the growth rate slowed over time and a second transplantation with bone marrow/mesenchymal stem cells has been used. There is limited experience in this area, so further trials are necessary[137,138]. The application of cellular reprogramming to create induced pluripotent stem cells (iPSCs) opens a new therapeutic approach.

Advances in gene editing technology bring the possibility of correcting the pathogenic variant. A recent approach involves the silencing of a dominant (gain of function) pathogenic variant, leading to allele suppression and converting the severe forms into a milder phenotype. Different strategies have been used: Antisense oligonucleotides, short interfering RNA, and hammerhead ribozymes. Another approach, gene addition therapy, involves the correction of the expression of deficient or absent alleles in affected cells. In cases where an abnormal collagen chain is produced and affects triple helix assembly, this method will not influence the phenotype. The efficiency of gene editing is still debatable, there are no data about the duration of the positive effects, and concerns regarding off-target effects, risks of an immune response, and genotoxicity are raised. Clinical trials are needed[126,139].

The combination of the CRISPR–Cas9 gene editing tool with induced pluripotent stem cells may improve therapeutic options. Jung *et al*[140] demonstrated the restoration of type I collagen expression in iPSCs in an OI patient corrected by the CRISPR–Cas9 system.

A new promising therapy is the chemical chaperone 4-phenylbutyrate (4-PBA), involved in protein folding and aggregation in ER. 4-PBA also has histone deacetylase inhibitor activity. Experimental studies reported the reduction of fracture rate and improvement of growth deficiency in animal OI models after 4-BPA treatment[141,142].

CONCLUSION

In recent decades, great progress has been made in identifying genes and molecular mechanisms underlying OI. These advances demonstrate that OI is an extremely heterogeneous collagen-related disease. The classical clinical Sillence classification is now partially revolute, and the involvement of different causative genes and the presence of different inheritance patterns generate challenges for genetic counseling. However, genetic classification allows an accurate identification of the inheritance for family planning, and offers the possibility of the development of genotype-based therapeutic approaches.

FOOTNOTES

Author contributions: Panzaru MC, Caba L wrote the manuscript draft; Florea A performed the literature research; Panzaru MC and Gorduza EV wrote the review, and Gorduza EV supervised the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Liu XF
L-Editor: A
P-Editor: Yu HG

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