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Osteogenesis imperfecta

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Abstract

Osteogenesis imperfecta is a phenotypically and molecularly heterogeneous group of inherited connective tissue disorders that share similar skeletal abnormalities causing bone fragility and deformity. Previously, the disorder was thought to be an autosomal dominant bone dysplasia caused by defects in type I collagen, but in the past 10 years discoveries of novel (mainly recessive) causative genes have lent support to a predominantly collagen-related pathophysiology and have contributed to an improved understanding of normal bone development. Defects in proteins with very different functions, ranging from structural to enzymatic and from intracellular transport to chaperones, have been described in patients with osteogenesis imperfecta. Knowledge of the specific molecular basis of each form of the disorder will advance clinical diagnosis and potentially stimulate targeted therapeutic approaches. In this Seminar, together with diagnosis, management, and treatment, we describe the defects causing osteogenesis imperfecta and their mechanism and interrelations, and classify them into five groups on the basis of the metabolic pathway compromised, specifically those related to collagen synthesis, structure, and processing; post-translational modification; folding and cross-linking; mineralisation; and osteoblast differentiation.

Introduction

The identification of the first gene for recessive osteogenesis imperfecta in 2006^{1,2} initiated a burst of exciting new information about the genetics and mechanism of this bone dysplasia.³ Osteogenesis imperfecta, or brittle bone disease, is a fairly common rare disorder (one in 15–20 000 births). This generalised connective tissue disorder has major manifestations in bone, leading to skeletal fragility and substantial growth deficiency.⁴ Previously, osteogenesis imperfecta was known as an autosomal dominant disorder caused by mutations in *COL1A1* and *COL1A2*, coding for the $\alpha 1(I)$ and $\alpha 2(I)$ chains of type I

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Declaration of interests

We declare no competing interests.

collagen, the most abundant protein of bone, skin, and tendon extracellular matrices. Although about 85–90% of cases are caused by structural or quantitative mutations in the collagen genes themselves, the disorder is now more fully understood as a predominantly collagen-related disorder.^{3,5} Seven recessive forms are caused by defects in genes whose protein products interact with collagen for folding or post-translational modifications. Two other rare defects mainly affect bone mineralisation, but also decrease collagen production. Now, the most recently identified genes could open a new chapter, with primary defects in osteoblast differentiation. Each discovery revealed a protein or pathway whose crucial importance for bone development had not been appreciated (see Orgel and colleagues⁶ for a review on bone composition and collagen-extracellular proteins interaction). The exciting advances in rare forms of the disorder sparked renewed interest in classic osteogenesis imperfecta with collagen defects, revealing changes in bone cell metabolism and development, and initiating a new era for diagnosis and potential treatment.

The classification evolved with the new genetic discoveries. The 1979 Sillence classification⁷ divided osteogenesis imperfecta into four types, from mild to lethal, on the basis of clinical and radiographic features.⁸ Identification of collagen defects showed that mild Sillence type I was related to quantitative deficiency of structurally normal collagen, whereas lethal (type II), severe (type III), and moderate (type IV) forms had mutations altering collagen structure.⁴ A genetic classification incorporated a new type for each defective gene. To make this information user friendly for clinicians and patients and to establish a structure for future development, we propose to group the genetic types on the basis of altered intracellular or extracellular metabolic pathways.

Diagnosis

The initial diagnosis is largely based on clinical and radiographic findings.^{7,8} Fractures from mild trauma, bowing deformities of long bones, and growth deficiency are the hallmark features. Dependent on age and severity, skeletal features can include macrocephaly, flat midface and triangular facies, dentinogenesis imperfecta, chest wall deformities such as pectus excavatum or carinatum, barrel chest, and scoliosis or kyphosis.³ Skeletal radiographs reveal generalised osteopenia, and some combination of long-bone bowing, undertubulation and metaphyseal flaring, gracile ribs, narrow thoracic apex, and vertebral compressions. Osteogenesis imperfecta is a generalised connective tissue disorder, whose findings often extend to non-skeletal features, including blue sclerae, hearing loss, decreased pulmonary function, and cardiac valvular regurgitation. Notably, the most common secondary features of the disorder are absent from newly recognised recessive forms, which generally have white sclerae, and normal cranial size, teeth, and hearing.³ Mild osteogenesis imperfecta can present a diagnostic challenge to discriminate from early onset osteoporosis in adults or physical abuse in children. Dual-energy x-ray absorptiometry (DXA) bone density provides useful, if not diagnostic, information in these cases, as does consultation with experts on connective tissue disorders.

In osteogenesis imperfecta caused by a collagen defect (types I–IV), bone histomorphometry reveals low bone volume and trabecular number, with high turnover kinetics,^{9,10} whereas histology is distinctive in types V and VI.^{11,12} This invasive test has been superseded by

molecular testing for all types, and measures of pigment epithelium-derived factor (PEDF) serum concentration for type VI. When possible, clinicians should do a full screen of osteogenesis imperfecta causative genes and identify carrier status or presence of second mutations to understand the complexity of the disorder rather than stopping the investigation when the first plausible mutation is identified. However, for economic reasons, a first screen for *COL1* genes is recommended in families with a single proband, followed by a complete sequence of the other osteogenesis imperfecta genes in case of negative result. When more than one child in a family is affected by the disorder, investigation of the whole osteogenesis imperfecta gene panel represents a better approach than waiting to rule out *COL1* genes first. A molecular diagnosis is very useful for counselling for prognosis, recurrence, and heritability, and for variable response to drugs.

Defects in collagen

Type I collagen is a heterotrimer, containing two $\alpha 1(I)$ and one $\alpha 2(I)$ chains. It is synthesised as a procollagen molecule, with N-terminal and C-terminal globular propeptides flanking the helical domain. The helical domains contain uninterrupted Gly-Xaa-Yaa triplets because the small glycine side chain fits in the internal helical space.

Procollagen chains assemble at their C-propeptides and fold toward the N-terminal. The unfolded chains are subjected to multiple post-translational modifications. Proline and lysine residues along the helical regions of both chains are hydroxylated by prolyl 4-hydroxylase 1 (which acts on the proline ring carbon-4) and lysyl hydroxylase 1 (LH1); hydroxylysine residues can subsequently be glycosylated.¹³ By contrast, prolyl 3-hydroxylase 1 (P3H1), acting as part of a complex with cartilage associated protein (CRTAP) and cyclophilin B (CyPB),¹⁴ hydroxylates the carbon-3 of discrete proline residues $\alpha 1(I)$ Pro986 and $\alpha 2(I)$ Pro707.¹⁵ Isomerisation of peptidyl prolyl bonds, crucial for proper collagen folding, is catalysed by specific peptidyl prolyl *cis-trans* isomerases (PPIase).¹⁶

The most common structural defects in type I collagen causing osteogenesis imperfecta are glycine substitutions in the helical domain (figure 1). Glycine substitutions delay helical folding, prolonging access time for modifying enzymes. Each α chain has a distinct genotype-phenotype relation. In the $\alpha 1(I)$ chain, substitutions with charged or branched side chains disrupt helix stability and are predominantly lethal. Substitutions in two major ligand binding regions near the carboxyl end of $\alpha 1(I)$ have exclusively lethal outcomes, pointing to crucial interactions between the collagen monomer and non-collagenous matrix proteins. In the $\alpha 2(I)$ chain, substitutions are mainly non-lethal; however, eight lethal clusters along the chain align with proteoglycan binding sites on collagen fibrils.⁴ Finally, less than 5% of mutations that cause classic osteogenesis imperfecta occur in the procollagen C-propeptide, impairing chain association or folding (figure 1).¹⁷

Collagen with a primary structural defect has more severe consequences for intracellular metabolism and matrix structure than does a reduced amount of normal collagen. Combined endoplasmic reticulum stress and mutant matrix leads to impaired maturation of bone-forming osteoblasts. Also, in the *Brl* mouse model for classic osteogenesis imperfecta, which is heterozygous for an $\alpha 1(I)$ Gly349Cys substitution, mesenchymal stem cells,

precursors to both osteoblasts and adipocytes, show increased plasticity to adipogenesis, although osteoblast number is not deficient.¹⁸ This evidence remains to be extended to patients.

Heterozygous null *COL1A1* alleles result in synthesis of a reduced amount (about half) of structurally normal collagen and cause the mildest form of the disorder.¹⁹ Homozygous null $\alpha 2(I)$ mutations cause symptoms ranging from severe osteogenesis imperfecta to a mild Ehlers-Danlos syndrome-like disorder that is associated with cardiac defects,^{20,21} whereas heterozygotes have no apparent osteogenesis imperfecta phenotype.²²

Processing defects

After secretion, procollagen molecules undergo an extracellular maturation process, in which the N-propeptides and C-propeptides are removed by specific proteases. After processing, the collagen helices are able to spontaneously assemble into fibrils in tissue, to be further stabilised by crosslinks. Mutations altering the propeptide cleavage sites cause interesting and specific variants of osteogenesis imperfecta.²³

The N-propeptide cleavage site is encoded by exon 6 in both *COL1A1* and *COL1A2*; it is cleaved by the metalloenzyme ADAMTS-2, which requires a helical substrate conformation. One cause of defective N-propeptide processing is so-called skipping of exon 6 at the RNA level—effectively removing the procollagen cleavage site—causing Ehlers-Danlos syndrome VII A if *COL1A1* is affected or Ehlers-Danlos syndrome VII B if *COL1A2* is affected (figure 1). Ehlers-Danlos syndrome type VII cases show tissue hyperlaxity, with severe joint hypermobility, congenital bilateral hip dislocation, ligamentous laxity causing scoliosis, and joint dislocations. It also involves mild osteopenia, resulting in fractures in some patients.²⁴ A second cause of defective N-propeptide processing implicates dominant mutations in the first 85 residues of the helical region of $\alpha 1(I)$ or $\alpha 2(I)$ collagen, which unfold the contiguous N-propeptide cleavage site, causing combined osteogenesis imperfecta and Ehlers-Danlos syndrome. Mutations in this region of *COL1A1* cause moderate to severe osteogenesis imperfecta, whereas the Ehlers-Danlos syndrome symptoms predominate from *COL1A2* mutations. Clinically, patients with combined osteogenesis imperfecta and Ehlers-Danlos syndrome have striking laxity of large and small joints, and paraspinal ligamentous laxity causes early and aggressive scoliosis. Congenital hip dislocation is also reported in combined *COL1A2* osteogenesis imperfecta and in Ehlers-Danlos syndrome. Dermal collagen fibrils are very thin, as in Ehlers-Danlos syndrome type VII.²⁵ A third type of defective N-propeptide processing has recessive inheritance, caused by mutations affecting *ADAMTS-2* activity (Ehlers-Danlos syndrome VIIC). This disorder is more severe than the other types of defective N-propeptide processing and is caused by defective processing of type II and type I collagen, characterised by extreme skin fragility, characteristic facies, joint laxity, droopy skin, umbilical hernia, and blue sclera.²⁶ In mice lacking both procollagen N-proteinase alleles, skin collagen fibrils revealed reduced diameter with ageing and bizarre curls in transverse sections.²⁷

Similarly, processing defects of the C-propeptide have a dominant form with substitutions in the cleavage site and a recessive form with defects in the processing enzyme.^{17,28–32} Quite

unexpectedly and paradoxically, these defects collectively lead to so-called high-bone-mass osteogenesis imperfecta (figure 1).²⁹ Dominant mutations in both residues (Ala-Asp) of the C-propeptide cleavage site in *COL1A1* and *COL1A2* have been reported,^{29,32} resulting in incorporation of pC-collagen into the extracellular matrix and collagen fibrils with irregular cross-sections.²⁹ Prepubertal children with *COL1A1* (Asp1219Asn) and *COL1A2* (Ala1119Thr) mutations have mild osteogenesis imperfecta with few fractures, normal stature, white sclerae, normal teeth, and increased DXA *Z* scores of 3 and 0 respectively, compared with the negative *Z* score usually reported for both dominant and recessive osteogenesis imperfecta. The bone tissue of children with these mutations showed substantial increases in mineralisation, beyond the standard hypermineralisation of bone with the disorder. *COL1A1* (Ala1218Thr) was reported in adults with scoliosis, normal stature, white sclerae, and raised DXA *Z* scores, whereas *COL1A2* (Asp1120Ala) causes joint laxity, blue sclerae, and DXA *Z* scores of 3-5. High bone mass in these patients was hypothesised to be caused by localisation of pC-collagen on the fibril surface, serving as nucleators of mineralisation.²⁹ Decreased type I C-propeptide trimer might also affect the phenotype, since its absence could affect bone vascularisation.³³

Cleavage of the C-propeptide is more complex than that of the N-propeptide, with four different C-proteases and modulation by an enhancer protein.³⁴⁻³⁷ Mutations of the major C-protease enzyme BMP1/mTLD result in more severe osteogenesis imperfecta than do substrate defects because these enzymes also process other procollagens and activate lysyl oxidase, the initiator of crosslinks.^{30,31} Knockout *Bmp1* mice have collagen with a barbed-wire appearance due to retention of the C-propeptide.³⁸ A mutant zebrafish revealed that BMP1 affects mainly the ability to generate mature collagen fibrils, rather than osteoblast development.³⁰ Notably, patients with a homozygous substitution in the BMP1 signal peptide have high bone mineral density that is similar to that in collagen substrate defects.³⁰ However, homozygous substitution (Phe249Leu) in the BMP1 protease domain had an osteoporotic outcome. In this situation, residual BMP1 activity probably accounts for the reduction in severity.³¹

Defects in collagen post-translational modification and folding

Procollagen undergoes several post-translational modifications during synthesis, which are important for procollagen folding, secretion, and extracellular matrix assembly and are cell, site, and temporally regulated. Most of these crucial processing steps occur in the endoplasmic reticulum. The identification of a multiprotein complex¹³ has helped researchers to further understand rare osteogenesis imperfecta forms and to identify a mechanism by which mutations in different proteins can cause clinically similar forms of the disorder.

The collagen prolyl 3-hydroxylation complex opened the floodgate to understanding rare forms of osteogenesis imperfecta. P3H1, the enzyme that causes 3-hydroxylation of $\alpha 1(I)$ Pro986 in type I collagen, was isolated³⁹ as part of a complex of three proteins in a 1:1:1 ratio of P3H1, CRTAP, and CyPB (figure 2).¹⁴ P3H1 is the catalytically active component, whereas CRTAP is a helper protein but does not have a catalytic domain. CRTAP is predominantly located in the endoplasmic reticulum, although a small amount is

secreted.⁴⁰ CyPB is a well known peptidyl-prolyl *cis-trans* isomerase. The *trans* proline configuration is required for protein folding; prolyl isomerisation is rate limiting for collagen folding.⁴¹ The precise function of collagen 3-hydroxylation is still unclear, although a role in collagen fibril formation has been proposed.⁴²

A null mutation in *CRTAP* causes osteogenesis imperfecta type VII, whereas a null mutation in *LEPRE1* (which encodes P3H1) causes type VIII, both of which can be severe to lethal and result in overmodification of the full collagen helical region.^{1,2,43} Affected individuals have an osteochondrodystrophy, since the complex is also expressed in cartilage, with neonatal fractures and broad undertubulated long bones, white sclerae, and rhizomelia (shortening of the proximal segment of the limbs). Individuals who live beyond infancy have notable growth deficiency, very low bone mineral density (Z -6), and bulbous metaphyses.⁴⁴ About half of *LEPRE1* cases have a west African founder allele found in Ghana and Nigeria and among African-Americans, which is almost uniformly lethal in homozygous form.⁴⁵ *CRTAP* and *LEPRE1* mutations always cause severely reduced to absent Pro986 3-hydroxylation, but whether the pathological defect is attributable to an absence of collagen 3-hydroxylation or an absence of the 3-hydroxylation complex is unclear.⁴⁶ A null mutation in either *LEPRE1* or *CRTAP* results in the absence of both proteins from mutant cells⁴⁷ because these proteins are mutually supportive in the complex, accounting for the similar clinical outcome of these gene defects.⁴⁷ *CRTAP* mutations can also cause renal or pulmonary abnormalities, probably because some CRTAP is secreted.⁴⁷ All cases with CRTAP or P3H1 defects share the biochemical feature of overmodified collagen α chains, because of a delay in collagen folding that allows excess hydroxylation and subsequent glycosylation of helical lysine residues.³ Positive biochemical tests for overmodification are also reported in dominant osteogenesis imperfecta caused by collagen defects.⁴

Mutations in the third member of the complex, cyclophilin B (encoded by *PPIB*), are biochemically and phenotypically distinct from P3H1 and CRTAP deficiency. These cases are quite rare, with only eight reported, and have either a moderate or a lethal phenotype (type IX).^{48,49} The affected individuals differ from P3H1 and CRTAP cases in that they do not have rhizomelia, although they share white sclerae and broad undertubulated long bones. In the infants with the lethal form of the disorder, $\alpha 1(I)$ Pro986 3-hydroxylation is reduced to about 30% of normal levels (but is never absent), although two children with moderate phenotypes and normal Pro986 3-hydroxylation have been independently reported.^{48,50} Furthermore, the amount of CRTAP and P3H1 protein is only slightly reduced in *PPIB*-null cells, suggesting that although CyPB is not required for 3-hydroxylation, it is needed for folding of the collagen helix through its PPIase activity.⁵⁰

The distinctive phenotypic consequences of CyPB deficiency are representative of its multiple interactions with non-collagenous proteins in the endoplasmic reticulum (figure 2).⁴⁹ The interaction between CyPB and LH1 was first appreciated through its effect on collagen modification in *PPIB*-null cells.⁵⁰ LH1 hydroxylates triple helical lysine residues, which is important both for glycosylation and for extracellular collagen cross-links during fibril formation. In the American quarter horse, a CyPB missense mutation (Gly6Arg) causes Ehlers-Danlos syndrome-like dermal symptoms. Although equine collagen has normal 3Hyp content, suggesting the complex functions normally, the collagen has reduced

hydroxylysine content.⁴⁹ Similarly, collagen synthesised by cells from a knockout *Ppib* mouse shows a tissue and residue specific pattern of changes in lysine hydroxylation and glycosylation, with an important common feature of reduced hydroxylation of the helical lysine 87 residue crucial for collagen crosslinking.⁵¹ Together, the data strongly support a direct effect of CyPB on LH1 activity. Thus, CyPB affects collagen both as the major PPIase for collagen folding, and in its support of LH1 activity, affecting collagen modification and crosslinking.

Three reports have been published for recessive mutations in *TMEM38B* (type XIV), two in Bedouins and one in an 11-year old Albanian girl.^{52–54} *TMEM38B* encodes TRIC-B, which forms a trimeric endoplasmic reticulum-membrane cation channel synchronised with inositol trisphosphate-mediated release of calcium (figure 2).⁵⁵ Since the *Tmem38B* knockout mouse was perinatally lethal, no skeletal phenotype was reported.⁵⁵ The Bedouin mutation predicts truncation of the protein whereas the Albanian defect was a large genomic deletion that included the *TMEM38B* gene. Affected Bedouin individuals have generalised osteopenia with multiple long bone fractures from birth and bowing deformities but without platyspondyly. Blue sclerae but normal teeth, facies, and hearing were reported.^{52,53} A similar phenotype was present in the Albanian girl, with the addition of mild hearing loss. Multiple proteins in the endoplasmic reticulum involved in collagen metabolism are calcium dependent, leading to an expectation of altered collagen modification.⁵⁵

Defects in collagen folding and crosslinking

Another rough endoplasmic reticulum-resident immunophilin is also crucial for normal collagen synthesis. The PPIase FKBP65 is encoded by *FKBP10* (figure 3).⁵⁶ As with CyPB, FKBP65 has both direct and indirect effects on procollagen through collagen modifying enzymes. Recessive defects in *FKBP10* cause a continuum of three previously distinct recessive syndromes.

FKBP65 deficiency was first shown to cause recessive osteogenesis imperfecta (type XI), ranging from progressive deforming, with long bone fractures, platyspondyly, and scoliosis, to moderate, with short stature and ambulation potential, all with normal sclerae and teeth.^{57,58} Second, *FKBP10* mutations cause Bruck syndrome 1, a distinctive disorder with severe osteogenesis imperfecta and congenital contractures of large joints, short stature, pterygia, and scoliosis.⁵⁹ The same *FKBP10* mutations occur with or without contractures, suggesting that they are allelic. The third outcome of FKBP10 mutations, Kuskokwim Syndrome, adds a disorder with only contractures to the previous FKBP10 phenotypic range of osteogenesis imperfecta or osteogenesis imperfecta with contractures.⁶⁰ Kuskokwim syndrome is a congenital contracture disorder with minor skeletal features, occurring uniquely in Yup'ik Eskimos in Alaska. Residual FKBP65 (about 5% of the amount in normal cells) in Kuskokwim syndrome is apparently sufficient to prevent substantial bone dysplasia.

Two sets of data led to the association of FKBP65 with lysyl hydroxylase 2 (LH2), the enzyme encoded by *PLOD2*, which hydroxylates collagen telopeptide lysines (figure 3). The first clue was biochemical, the alteration of collagen crosslinks.⁶¹ In bone, hydroxylation of telopeptide lysines is necessary to generate cross-links between collagen molecules to

provide stability and tensile strength to fibrils.⁶² Patients with Bruck syndrome 1 with either *FKBP10* or *PLOD2* mutations have reduced hydroxylysine-derived cross-links in bone collagen.⁵⁹ The second clue was that cells with the *FKBP10* mutation deposit a reduced amount of collagen into the extracellular matrix.⁵⁸ Collagen telopeptide lysine hydroxylation in mutant cells was reduced to a minimum. These data support a direct interaction between FKBP65 and LH2, perhaps to isomerise the peptidyl-prolyl bonds in LH2. At present, no data support a direct role for the FKBP65 PPIase activity in collagen helical folding.

HSP47 is a collagen-specific chaperone that is resident in the endoplasmic reticulum and is encoded by *SERPINH1*. It has an RDEL recognition site to mediate shuttling of the protein between the endoplasmic reticulum and Golgi, and it binds only to triple helical collagen (figure 3).⁶³ It functions to stabilise folded collagen and to mark it for transfer to the cis-Golgi. *Serpinh1* knockout mice are embryonic lethal.⁶⁴ Their cells display intracellular collagen aggregation, delayed secretion, and abnormal fibrils.⁶⁵ Not surprisingly, both *SERPINH1* mutations reported—in dachshunds and a child with severe recessive osteogenesis imperfecta (type X)—are homozygous missense mutations, which probably have some residual activity, rather than null defects.^{66,67} The child lived for 3 years and had blue sclerae, dentinogenesis imperfecta, and atypical features such as skin bullae, pyloric stenosis, and renal stones. His collagen had increased sensitivity to proteases, suggesting imperfect folding.

Defects in ossification and mineralisation

Types V and VI osteogenesis imperfecta share the distinction of causing primary defects in endochondral bone ossification or mineralisation. Dominantly inherited type V and recessively inherited type VI were delineated clinically, on the basis of phenotypic, radiographic, and histological features, and normal type I collagen posttranslational modification.^{11,12} Whole exome sequencing revealed causative mutations in the interferon-induced transmembrane protein 5 (*IFITM5*) for type V^{68,69} and *SERPINF1* genes for type VI^{70,71} (figure 4). Although mutations in these genes have opposite effects on mineralisation—with increased ectopic ossification in type V and reduced bone mineralisation in type VI—their metabolic pathways intersect, suggesting that the proteins have a functional connection.

Unique among osteogenesis imperfecta types, all patients with type V have the same heterozygous mutation in *IFITM5*, a point mutation in the 5'-UTR (c.-14C→T), which generates a novel start codon and adds five residues to the N-terminal of the protein. Affected individuals have moderately severe bone dysplasia with a variable combination of distinctive features, including ossification of the forearm interosseous membrane, radial head dislocation, and a subphyseal metaphyseal radiodense band.^{72,73} More than half of patients with type V develop hyperplastic callus during fracture healing. Scleral hue is variable whereas teeth are normal. All patients with type V have distinctive mesh-like lamellation on bone histology. Type V has the paradoxical association of an osteoporotic phenotype from a defect in trabecular osteoblasts and exuberant bone formation in hypertrophic callus, affecting periosteal bone. These data suggest that *IFITM5* functions differently in trabecular versus periosteal bone.

IFITM5, also known as bone-restricted IFITM-like (BRIL), is a member of the IFITM family. It has a single transmembrane domain with an extracellular C-terminus. On the cytoplasmic side, BRIL is attached to the membrane through palmitoylation of cysteines 52 and 53 (figure 4). It shares only 30% amino acid identity with other family members and is not induced by interferon. It is localised predominantly to the osteoblast plasma membrane and expressed throughout life, although expression decreases with age. BRIL is not detectable in either chondrocytes or osteocytes;⁷⁴ low expression occurs in fibroblasts.

Neither *Ifitm5* knockout mice⁷⁵ nor people with deletions of one BRIL allele manifest bone dysplasia. Therefore, the likely molecular basis of osteogenesis imperfecta type V is a gain of function. Overexpression of *Ifitm5* in vitro increases alkaline phosphatase expression and mineral deposition, whereas silencing has opposite effects.⁷⁶ The only known BRIL binding partner in osteoblasts is FKBP11; BRIL binding disrupts the interaction of CD9 with FKBP11–CD81. Since the CD9–FKBP11 complex increases expression of interferon-induced genes, type V might have an immune component.⁷⁷ Furthermore, BRIL can regulate calcium binding through C-terminal residues, which could affect both mineral formation and signal transduction pathways regulating bone development.⁷⁸

Compromised mineralisation also occurs in patients with type VI osteogenesis imperfecta who have homozygous or compound heterozygous null mutations of *SERPINF1*, which encodes PEDF. The clinical course of these patients is distinctive, with fractures generally absent in the first year, followed by a severe progressive deforming bone dysplasia, with frequent long bone fractures, vertebral compressions, and severely reduced bone mineral density. Bone histology reveals an increased amount of unmineralised osteoid and a so-called fish-scale lamellar pattern under polarised light.^{70,71,79} The increased mineral lag time underlies the low response of type VI to bisphosphonates.⁸⁰

PEDF belongs to the Serpin family of serine protease inhibitors but does not have protease inhibitory activity. It is a potent anti-angiogenic factor⁸¹ expressed by a wide range of cells, including chondrocytes throughout the growth plate, osteoblasts, and mesenchymal stem cells.⁸² In bone, PEDF functions at many levels to maintain bone homeostasis and regulate osteoid mineralisation. A *Serpinf1* knockout mouse replicated the reduced bone volume and unmineralised osteoid typical of type VI.⁸³ PEDF positively affects osteoblast development by favouring the expression of osteogenic genes and mineral deposition. It inhibits osteoclast maturation by stimulating osteoprotegerin expression.⁸⁴ Thus, absence of PEDF increases osteoclast number and bone resorption by favouring RANKL binding to the osteoclast RANK receptor.⁸⁵

That PEDF interacts with two sites on type I collagen is also relevant.⁸⁶ One binding site overlaps the heparin and heparan sulphate proteoglycan binding site with the $\alpha 1(I)$ C-terminal major ligand binding region. The second collagen-binding site, in the $\alpha 1(I)$ N-terminal, overlaps integrin collagen-binding sites. Importantly, an intact collagen-binding site on PEDF is required for its anti-angiogenic activity (figure 4).

A heterozygous *IFITM5* mutation that connects types V and VI has been delineated.⁸⁷ The Ser40Leu substitution interferes with modification of the nearby BRIL palmitoylation sites.

⁸⁸ This mutation causes severe progressive deforming osteogenesis imperfecta and bone histology typical for type VI, but none of the clinical or radiographic findings of type V. Proband fibroblasts and osteoblasts do not secrete PEDF, although serum PEDF concentrations are normal. Conversely, osteoblasts with the *IFITM5* mutation causing type V have increased *SERPINF1* expression. These data further support the type V *IFITM5* mutation as having a gain-of-function mechanism, in which the PEDF pathway is overactivated, whereas Ser40Leu probably causes loss of a BRIL function important for *SERPINF1* expression (figure 4).⁸⁷

Defects in osteoblast development

Three genes implicated in osteoblast differentiation have been associated with osteogenesis imperfecta phenotypes: *WNT1* (type XV), *CREB3L1* (type XVI), and *SP7* (type XII). Defects in these genes either cause, or are expected to cause, a reduction in type I collagen expression. The reported data support early onset osteoporosis but are still accumulating for the cause of osteogenesis imperfecta. The relation of these gene defects to collagen might simply be quantitative, resulting in osteopenia that combines with other manifestations of impaired osteoblast differentiation.

Of the three genes, *WNT1* has the most supportive data for osteogenesis imperfecta. Wnts are a family of secreted glycoproteins, whose binding to transmembrane receptors LRP5 and LRP6 and Frizzled initiates a complex intracellular signalling pathway. In the canonical pathway, Wnt binding enables cytosolic β -catenin to escape proteasomal destruction and be translocated into the nucleus, where it activates expression of several genes implicated in bone formation. Heterozygous *WNT1* mutations were identified in patients presenting as early onset osteoporosis.⁸⁹ Homozygous non-sense, missense, frameshift, or splicing mutations in *WNT1* occur in patients with severe osteogenesis imperfecta, with short stature, frequent fractures, and vertebral compressions. Several patients with *WNT1* defects have brain malformations. Some *WNT1* mutations impair activation of the canonical pathway and mineralisation by osteoblasts in vitro.^{90–93} By contrast, *Wnt1* knockout mice have a severe neurological defect but do not have skeletal manifestations.⁹⁴ *Wnt1* expression in osteoblasts, osteocytes, haemopoietic progenitor cells, and B cells support a complex regulatory role for *WNT1* in bone formation.⁹¹

The second gene functioning predominantly at the osteoblast level is *CREB3L1*, encoding the endoplasmic reticulum-stress transducer old astrocyte specifically induced substance (OASIS). After proteolysis, the N-terminal domain of OASIS translocates into the nucleus and activates the *COL1A1* promoter.⁹⁵ An Oasis-null mouse has severe osteopenia with reduced bone volume, trabecular thickness, and growth retardation. *Oasis*^{−/−} osteoblasts have decreased *Col1a1* expression and expanded endoplasmic reticulum.⁹⁵ However, in fibroblasts from siblings with lethal bone dysplasia, a large homozygous deletion including *CREB3L1*, did not cause qualitative or quantitative defects of type I collagen or raised endoplasmic reticulum-stress markers.⁹⁶ A clear relation of *CREB3L1* to the osteogenesis imperfecta phenotype awaits additional patient mutations and osteoblast investigation.

The third gene with a potential osteoblast mechanism is *SP7*, which encodes osterix and is a target gene of the Wnt pathways. A homozygous *SP7* mutation, putatively truncating a fifth of Osterix, was reported in severe recessive osteogenesis imperfecta.⁹⁷ This gene awaits functional molecular and biochemical data.

Osteogenesis imperfecta classification

Both clinical and genetic classifications have emerged to encompass the rare forms of osteogenesis imperfecta since most new genes do not have specific diagnostic features. In the clinical classification, the new forms of the disorder were merged into Sillence types I to IV by clinical severity. For example, type II osteogenesis imperfecta, the perinatal lethal form, included lethal collagen mutations and some *CRTAP*, *LEPRE1*, *PPIB*, *SERPINH1*, and *SP7* mutations.⁹⁸ Some clinical classifications retained types V, VI, and VII, originally delineated clinically.⁹⁹ This classification results in many incongruous situations, including retyping of an individual by severity during their lifetime and siblings with different osteogenesis imperfecta types. In the same type, individuals would have dominant or recessive inheritance, confusing genetic counselling and hindering research on the disease mechanism and response to therapy.

In a genetic classification, Sillence types are used only for collagen mutations and the numeration is continued for each new gene discovery.⁵ This pattern eliminates the issues cited above and provides a better arrangement for research and clinical management than that of a clinical classification. However, a genetic classification has the disadvantage of an evolving list, which can be difficult for geneticists and parents to use beyond a dozen types.

To satisfy both clinical and genetic requirements, we propose that a functional metabolic classification will have the broadest usefulness and still allow retention of genetic type numeration (table). A similar regrouping of Ehlers-Danlos syndrome by function was successful for both clinicians and families.¹⁰⁰ In this plan, genes whose products function in the same pathway, and are likely to have shared mechanisms, are arranged in five functional groups: group A, primary defects in collagen structure or processing (*COL1A1*, *COL1A2*, and *BMP1*); group B, collagen modification defects (*CRTAP*, *LEPRE1*, *PPIB*, and *TMEM38B*); group C, collagen folding and cross-linking defects (*SERPINH1*, *FKBP10*, and *PLOD2*); group D, ossification or mineralisation defects (*IFITM5* and *SERPINF1*); and group E, defects in osteoblast development with collagen insufficiency (*WNT1*, *CREB3L1*, and *SP7*). The functional genetic classification could be usefully supplemented by a parallel clinical severity score for physical rehabilitation on the basis of a proposed scheme.¹⁰¹

Medical management of osteogenesis imperfecta

Osteogenesis imperfecta is best managed by a multidisciplinary team. Physical rehabilitation by a therapist with experience of the disorder is arguably the most important contribution to function. The combination of fragile bones, weak muscle, and cycles of fracture and disuse creates substantial challenges for a patient to attain and maintain gross motor skills, especially walking.¹⁰² Physiotherapy and hydrotherapy focused on muscle strength and joint range of motion are crucial to maximise an individual's function and independence.¹⁰³ Most

individuals with severe osteogenesis imperfecta can attain self-care, transfer (an ability to transfer independently between their bed, toilet, and chair), and domestic skills needed for independent living, educational, and occupational success.¹⁰⁴ Individuals with mild osteogenesis imperfecta can function at a very high level, often excluding only contact sports.¹⁰⁵

Pulmonary function impairment is the major cause of morbidity and mortality in osteogenesis imperfecta.¹⁰⁶ Loss of pulmonary function is related to scoliosis greater than 60°, ¹⁰⁷ and rib cage and pectal deformity, which alter respiratory muscle and chest wall action,¹⁰⁸ contributing to respiratory infections and insufficiency. Even paediatric patients without scoliosis show progressive restrictive pulmonary disease, supporting a primary cardiopulmonary effect of abnormal collagen.¹⁰⁹ The main cardiac manifestations are valvular, especially aortic and mitral regurgitation.^{110,111}

Audiology examination should start in childhood, since hearing loss begins in the first or second decades in about 5% of patients.¹¹² Hearing loss is mostly mixed sensorineural and conductive, with a few cases having pure conductive or sensory loss.¹¹³ Patients might need hearing aids or cochlear implants. Stapedectomy provides restoration of conductive loss in long-term follow-up.¹¹⁴

Skull base abnormalities, including platybasia, basilar invagination, and basilar impression, are prevalent in patients with height *Z* score less than -3.¹¹⁵ Basilar impression, in which the foramen magnum rim folds into the skull, is the most serious neurological complication of the disorder.¹¹⁶ It can lead to compression of the brainstem, hydrocephalus, and syrinx. Bisphosphonate treatment has not affected the incidence of basilar impression.¹¹⁷

Present and prospective drug therapies

Bisphosphonates, antiresorptive drugs, which are synthetic analogues of pyrophosphate, are widely used to treat children with osteogenesis imperfecta. Bisphosphonates are deposited on the surface of bone, where their endocytosis by precursor or mature osteoclasts induces cell death (apoptosis). Thus, treatment aims to increase bone volume by counteracting the high turnover cellular status of bone in classic osteogenesis imperfecta. The new bone would still contain defective collagen in the classic types of the disorder, but the hypothesis behind the treatment is that an increased volume of bone (even of impaired quality) would be beneficial to bone strength. Bisphosphonates have a decade long half-life in bone, and drug effects on bone density persist for years after treatment cessation.

Most children with osteogenesis imperfecta have positive vertebral effects, including increased areal bone density DXA *Z* score of about 1.5 SD in the first treatment year and improved vertebral compressions.¹¹⁸ Increased vertebral height expands thoracic volume but has negligible effects on scoliosis,¹¹⁹ which lends support to a pathology model in which scoliosis in osteogenesis imperfecta is mainly driven by laxity of spinal ligaments. Two studies reported that maximum bone density and histology benefits are obtained after 2–3 years of treatment.^{120,121} Whether treatment should be paused at 3 years with careful follow-up of bone density and individualised restarting of treatment at later intervals, or

whether, after an initial 3 year regimen, children should be treated at a lower bisphosphonate dose until epiphyseal closure because anecdotal long bone fractures have been reported at the juncture of treated and untreated bone, remains an open question.¹²² The US National Institute of Health clinical experience has not included junctional fractures in children after bisphosphonate is discontinued.

The major intent of administration of bisphosphonates in osteogenesis imperfecta is to decrease fractures. Controlled trials are equivocal about reduction of long bone fractures,^{118,123} requiring use of unspecified adjustment factors to obtain changes in relative risk. Furthermore, meta-analyses, including two Cochran reviews in 2008 (403 patients)¹²⁴ and 2014 (819 patients)¹¹⁸ and a separate analysis of only placebo-controlled trials (424 patients total),¹²⁵ did not support a statistically significant effect of bisphosphonates on fractures in osteogenesis imperfecta. Supporters of prolonged treatment have raised the question of whether the studies had adequate power to detect a fracture decrease.^{118,124,125} In view of the number of patients in the meta-analyses, the effects on fracture of bisphosphonate administration would not be the robust improvement that patients and their caregivers are often told. A likely explanation for the equivocal reduction of fractures, despite a clear increase in bone mineral density, is that bone quality is reduced by bisphosphonate administration, as seen in animal studies, causing increased bone brittleness.¹²⁶ Long-term inhibition of osteoclasts leads to non-dynamic bone, in which microcracks are often not repaired. Microcracks and foci of retained mineralised cartilage from cyclic bisphosphonate infusions can facilitate crack propagation.¹²⁷ Studies of use of risedronate in children¹²⁸ or adults¹²⁹ showed a moderate improvement in fractures in children given the drug for more than 3 treatment years, but no difference in adult fracture rate. Similarly, treatment of adults with teriparatide showed benefit for only mildly affected patients, leaving adult treatment options sparse.¹³⁰ Controlled trials^{118,123} also have not supported improved mobility or pain status with bisphosphonates; despite anecdotal reports of bone pain relief, only increased activity endurance was reported.

Drugs with anabolic action on bone formation are undergoing testing in animal models of osteogenesis imperfecta and paediatric trials are anticipated. This mechanism is supported by previous paediatric trials of recombinant human growth hormone,^{10,131} which showed improved bone histology and bone mineral density in linear growth responders. The novel drugs are both antibodies, one to sclerostin,¹³² a negative regulator of bone formation in the Wnt pathway, and one to transforming growth factor- β ,¹³³ a coordinator of bone remodelling produced by osteoblasts. Treatment of *Brtl* mice with Scl-AB increases bone mass and load to fracture without inhibiting bone turnover. Importantly, tissue brittleness, a hallmark feature of the disorder, is decreased.¹³² Transforming growth factor- β neutralising antibody increases bone mass while reducing bone turnover in *Crtap* knock-mice and *Col1a2*^{+/G610C} dominant mice; bone load to fracture was improved but brittleness was not changed.¹³³

Orthopaedic surgery

Placement of an intramedullary telescoping rod in a long bone can stabilise a severe fracture, provide internal support for healing after correction of bone deformity, or interrupt fracture

or disuse cycles.¹³⁴ The Fassier-Duval rod aims to be minimally invasive, with a single entry point, and does not require arthrotomies.¹³⁵ Correction of deformity with Fassier-Duval rods is associated with improved ambulation.¹³⁵ Telescoping rods have a substantial incidence of migration, perhaps due to poor bone material quality.¹³⁶ Non-expanding Kirchner wires are suited to severe osteogenesis imperfecta types with slow growth.¹³⁷

Ageing and walking in patients with osteogenesis imperfecta contributes to joint osteoarthritis. Hip and knee arthroplasty are increasingly frequent in adults; the best results involve custom implants based on computer-assisted design.¹³⁸

Scoliosis in osteogenesis imperfecta is not amenable to bracing. Spinal fusion is generally done to stabilise and partly correct curvature greater than 50°. Standard approaches involve posterior fusion with Harrington instrumentation¹³⁹ or preoperative correction with halo traction followed by instrumented fusions.¹⁴⁰ However, laxity of spinal ligaments contributes to gradual loss of curve correction.

Conclusions

An exciting series of discoveries has rapidly advanced understanding of osteogenesis imperfecta and has identified genes whose importance for bone development was not previously appreciated. Common themes have emerged for dominant and recessive forms, including collagen-related mechanisms, abnormal mineralisation, osteoblast signalling, endoplasmic reticulum-stress, and cell-cell and cell-matrix signalling. Rare osteogenesis imperfecta types are prompting investigators to re-examine old themes, such as collagen modification, folding, and cross-linking. At present, availability of exome sequencing and advances in bone metabolism hold the prospect to identify all the remaining causes of the disorder and herald a new era in osteogenesis imperfecta diagnosis and therapeutics.

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Figure 1: Mutations in specific positions along type I procollagen molecule cause distinct clinical phenotypes

Mutations affecting the helical region of the α chains and the C-propeptide domain cause classic osteogenesis imperfecta, including the osteogenesis imperfecta/Ehlers-Danlos syndrome variant, which is caused by substitutions in the N-anchor domain. Molecular defects in the N-propeptide cleavage site cause Ehlers-Danlos syndrome VII A/B and in the C-propeptide cleavage site cause high bone mass osteogenesis imperfecta. Hexagons represent sugar molecules linked to hydroxyl lysine residues. OH=hydroxyl group linked to proline or lysine residues.

Figure 2: Proteins involved in type I procollagen post-translational modification and folding in the endoplasmic reticulum

Prolyl 3-hydroxylase, cartilage associated protein, and cyclophilin B act as a trimeric complex for hydroxylation of the 3-carbon position of the $\alpha 1(I)$ Pro986 and $\alpha 2(I)$ Pro707 proline residues. Cyclophilin B also affects the activity of lysyl hydroxylase 1, which hydroxylates lysine residues in the helical region of type I procollagen. The regulation of calcium ion concentration in the endoplasmic reticulum is relevant to procollagen post-translational modification because of its role in modulating calreticulin interaction with cyclophilin B and with protein disulphide isomerase. Protein disulphide isomerase complexes with prolyl 4-hydroxylase to hydroxylate the 4-carbon position of proline residues located in the Y-position of the repetitive collagenic triplet (Gly-X-Y).

Figure 3: Proteins affecting procollagen intracellular trafficking and extracellular crosslinking
Heat shock protein 47 is a specific collagen I chaperone, binding to the triple helical collagen domain in the endoplasmic reticulum, preventing aggregation, and facilitating its trafficking to the Golgi. An RDEL signal will then guide the return of heat shock protein 47 to the endoplasmic reticulum. FK506 binding protein 65 is a peptidyl prolyl cis-trans isomerase known to affect the activity of lysyl hydroxylase 2, the enzyme which hydroxylates lysine residues in the N-telopeptides and C-telopeptides that are crucial for crosslink formation in the extracellular matrix. The question marks refer to probable but not yet proven interactions.

Figure 4: Proteins involved in mineralisation of the collagen extracellular matrix

The transmembrane protein—bone restricted interferon induced transmembrane protein-like—regulates the expression of pigment epithelium derived factor, an important collagen-binding protein regulating bone homeostasis and osteoid mineralisation, which also has strong anti-angiogenic functions by an unknown mechanism. *SERPINF1* is the gene for pigment epithelium derived factor. The question marks refer to the presence of other factors in this pathway, which are not yet discovered. The plus and minus signs refer to increased and decreased transcription of the *SERPINF1* gene. S40L refers to the *IFITM5* mutation Ser40Leu.

Table:

Classification of classic dominant and new recessive forms of osteogenesis imperfecta

	OMIM number	Locus	Gene symbol	Silence type	Clinical variants	Protein	Main location	Bone deformity	Sclerae	Hearing loss	Dentinogenesis imperfecta	Other typical features
Defects in collagen synthesis, structure, or processing (group A)												
Autosomal dominant	166200	17q21.33	<i>COL1A1</i>	I	NA	Collagen type I, alpha 1	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	..
Autosomal dominant	166210	17q21.33	<i>COL1A1</i>	II	NA	Collagen type I, alpha 1	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	..
Autosomal dominant	259420	17q21.33	<i>COL1A1</i>	III	NA	Collagen type I, alpha 1	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	..
Autosomal dominant	166220	17q21.33	<i>COL1A1</i>	IV	OI/EDS and HBM/OI	Collagen type I, alpha 1	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	Type IV OI/EDS is due to mutations at the first 85 aminoacids of $\alpha 1(I)$; HBM/OI is caused by mutations blocking C-propeptide processing
Autosomal dominant	166200	7q21.3	<i>COL1A2</i>	I	NA	Collagen type I, alpha 2	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	..
Autosomal dominant	166210	7q21.3	<i>COL1A2</i>	II	NA	Collagen type I, alpha 2	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	..
Autosomal dominant	259420	7q21.3	<i>COL1A2</i>	III	NA	Collagen type I, alpha 2	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	..
Autosomal dominant	166220	7q21.3	<i>COL1A2</i>	IV	OI/EDS and HBM/OI	Collagen type I, alpha 2	Extracellular matrix	Rare to very severe	Normal, grey to dark blue	Absent to common	Absent to common	Type IV OI/EDS is due to mutations at the first 85 aminoacids of $\alpha 2(I)$; HBM/OI is caused by mutations blocking C-propeptide processing
Autosomal recessive	614856	8p21.3	<i>BMP1</i>	XIII	NA	Bone morphogenic protein 1/procollagen C proteinase	Pericellular environment	Mild to severe	Normal	Absent	Absent	Unilateral hernia, HBM
Defects in collagen modification (group B)												
Autosomal recessive	610682	3p22.3	<i>CRTAP</i>	VII	NA	Cartilage- associated protein	Endoplasmic reticulum	Severe rhizomelia	Normal, grey	Absent	Absent	..
Autosomal recessive	610915	1p34.2	<i>LEPRE1 / P3H1</i>	VIII	NA	Leucine proline-enriched proteoglycan 1/prolyl 3-hydroxylase 1	Endoplasmic reticulum	Severe rhizomelia	Normal	Absent	Absent	..
Autosomal recessive	259440	18q22.31	<i>PP1B</i>	IX	NA	Peptidylprolyl isomerase B/cyclophilin B	Endoplasmic reticulum	Severe	Grey	Absent	Absent	..
Autosomal recessive	615066	9q31.2	<i>TNFRM38B</i>	XIV	NA	Transmembrane protein 38 B	Endoplasmic reticulum membrane	Severe	Normal to blue	Absent	Absent	..
Defects in collagen folding and cross-linking (group C)												
Autosomal recessive	613848	11q13.5	<i>SERPINF1</i>	X	NA	Serpin peptidase inhibitor, clade H, member 1/heat shock protein 47	Endoplasmic reticulum	Severe	Blue	Absent	Present	Skin blisters and bullae at birth, inguinal hernia
Autosomal recessive	610968	17q21.2	<i>FABP10</i>	XI	NA	FXS06 binding protein 65	Endoplasmic reticulum	Mild to severe	Normal, grey	Absent	Absent	Variable congenital contractures, encompasses Bruck and Kusakovim syndromes
Autosomal recessive	609220	3q24	<i>PLD12</i>		NA	Procollagen- lysine, 2-oxoglutarate 5-deoxygenase 2	Endoplasmic reticulum	Moderate to severe	..	..	..	Progressive joint contractures
Defects in bone mineralisation (group D)												
Autosomal dominant	610967	11p15.5	<i>HPTM5</i>	V	NA	Interferon- induced transmembrane protein 5	Plasma membrane	Variable	Normal to blue	Infrequent	Absent	Ossification of the forearm interosseous membrane, radial head dislocation, subphyseal metaphyseal radiolucense band
Autosomal recessive	613982	17p13.3	<i>SERPINF1</i>	VI	NA	Pigment epithelium-derived factor	Extracellular matrix	Moderate to severe	Normal	Absent	Absent	Normal at birth, unmineralised osteoid, fish scale appearance of lamellar bone pattern, raised ALP, loss of serum PEP
Defects in osteoblast development with collagen insufficiency (group E)												
Autosomal recessive	613849	12q13.13	<i>SPT7</i>	XII	NA	Transcription factor 70sterix	Nucleus	Severe	Normal	Absent	Absent	Delayed tooth eruption, midface hypoplasia
Autosomal recessive	615220	12q13.12	<i>WNT1</i>	XV	NA	Wingless-type MMTV integration site family, member 1	Extracellular matrix	Severe	White	Absent	Absent	Possible neurological defects
Autosomal recessive	616229	11p11.2	<i>CXEB3L1</i>	XVI	NA	cAMP responsive element binding protein 3 like 1	Endoplasmic reticulum membrane	Severe	..	..	..	..

OMIM=Online Mendelian Inheritance in Man. NA=not applicable. OI=osteogenesis imperfecta. EDS=Ehlers-Danlos syndrome. HBM=high bone mass. ALP=alkaline phosphatase. PEDF=pigment epithelium-derived factor. MMTV=mouse mammary tumour virus.