

Below are two of the most widely regarded posts about Late Onset OI:

The links have been left intact, there will be a lay-summary in the FAQ

Osteogenesis Imperfecta

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ABSTRACT

Osteogenesis imperfecta (OI, or Brittle Bone Disease) is a clinically and genetically heterogeneous group of heritable disorders of connective tissue. The incidence of forms recognizable at birth is 1:10-20,000. The hallmark feature of OI is bone fragility, with susceptibility to fracture from minimal trauma, as well as bone deformity and growth deficiency. OI has multiple secondary features, including macrocephaly, blue sclerae, dentinogenesis imperfecta, hearing loss, neurological defects (macrocephaly and basilar invagination), and cardiopulmonary complications (the major cause of mortality directly related to OI). The current paradigm of OI is that of a collagen-related disorder. The classical Sillence types of OI (types I-IV) with autosomal dominant inheritance comprise about 80-85% of cases and are caused by mutations in the genes that encode type I collagen, *COL1A1* and *COL1A2*. These types encompass the full spectrum of OI severity, from perinatal lethal type II to progressively deforming type III to mild and diagnostically delayed type I. The rare forms of OI (types V-XVIII) delineated in the last decade have (except for type V and some XV) autosomal recessive inheritance and are caused by mutations in genes whose protein products interact with collagen for post-translational modification or folding. OI, regardless of etiology, requires clinical management and genetic analysis. Most individuals with OI have significant physical disabilities. The diagnostic work-up focuses on the skeletal system, including age-specific physical exam, a thorough family pedigree, radiographic examination, and DEXA. Differential diagnosis (child maltreatment, thanatophoric dysplasia, achondrogenesis type I, campomelic dysplasia, hypophosphatasia, osteoporosis) varies with patient age and OI severity. Genetic counseling, nonsurgical (e.g., rehabilitation, bracing, splinting), surgical, and pharmacological (bisphosphonates, anti-RANK ligand antibody, recombinant human parathyroid hormone analog, growth hormone) management are essential components of complete care for individuals who have OI. Fractures should be evaluated with standard x-rays and managed with

reduction and realignment, as needed, to prevent loss of function and to interrupt a cycle of refracturing. Two pharmacologic treatment modalities target osteoclast bone resorption.

Bisphosphonates (synthetic analogs of pyrophosphate) induce osteoclast apoptosis. Maximum effects on bone histology and density occur within the first year following treatment. Meta-analyses do not support significant reduction in long bone fractures in bisphosphonate-treated children. Anti-RANK ligand antibody improves bone mineral density in individuals with OI types I, III, IV and VI without accumulating in the bone matrix. Disturbance of calcium homeostasis is a clinically significant side effect. Anabolic therapy with growth hormone to ameliorate short stature in OI is successful for type I and about half of type IV OI children; responders also have improved bone histology, increased bone density and fewer fractures. Two antibody-based drugs with anabolic action on bone: anti-sclerostin, a negative regulator of bone formation in the Wnt pathway, and anti-TGF- β , a coordinator of bone remodeling produced by osteoblasts, have shown promising efficacy in early phase clinical trials and animal studies, respectively. Overall, a multidisciplinary approach to management of this set of disorders is most beneficial, with care centered on maximizing patient quality of life. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

Osteogenesis imperfecta (OI), also known as Brittle Bone Disease, is a clinically and genetically heterogeneous group of heritable disorders of connective tissue. The hallmark feature of OI is bone fragility, with a tendency to fracture from minimal trauma or from the work of bearing weight against gravity. In the more severe forms of the disorder, the bones are deformed as well as fragile. Most individuals with OI have significant physical disabilities. Affected persons also exhibit an array of associated features, including short stature, macrocephaly, blue sclerae, dentinogenesis imperfecta, hearing loss and neurological and pulmonary complications. Autosomal dominant OI types occur at comparable frequency in different genders, races, and ethnic groups. Various recessive OI types occur at higher frequency in populations in which founder mutations have been identified: type VII (*CRTAP*; First Nations in Ontario, Canada) type VIII (*P3H1*; West Africa), type XI (*FKBP10*; Turkey), Type XIV (*TMEM38B*; Bedouins), Type XV (*WNT1*; Hmong group in Vietnam and China).

Historically, osteogenesis imperfecta has been viewed as an autosomal dominant disorder of type I collagen, the major protein component in the extracellular matrix of bone. In the past decade, the OI paradigm has undergone a major shift with the identification of autosomal recessive forms. The

etiology of recessive OI types involves molecules that modify or interact with collagen post-translationally or are involved in osteoblast differentiation. These include proteins involved in bone mineralization, BRIL and PEDF; proteins involved in collagen modification and processing, CRTAP, P3H1 and CyPB (three components of the endoplasmic reticulum-resident collagen prolyl 3-hydroxylation complex), the chaperone HSP47, the foldase FKBP65, and the processing enzyme BMP-1; proteins involved in osteoblast differentiation SP7, WNT1 and Oasis (transcription factors), TRIC-B (a cation channel), the chaperone SPARC and the intramembrane regulatory protease S2P. OI, regardless of etiology, requires clinical management and genetic analysis. The incidence of forms of OI recognizable at birth is 1:10-20,000, with about equal incidence of mild forms that are not recognizable until later in life (1). OI and Marfan Syndrome share the distinction of being the most common heritable connective tissue disorders.

CLINICAL CLASSIFICATION AND PHENOTYPE

David Sillence formulated the classification currently in use for osteogenesis imperfecta in 1979 (2). Since type I collagen defects were not known to cause OI at that time, the Sillence Classification is based on clinical and radiographic features. The clinical spectrum of OI ranges from perinatal lethal to a mild form that can present in middle-aged adults as premature osteoporosis. In the past decade's discovery of 16 genes other than *COL1A1* and *COL1A2* have expanded the genotypic and phenotypic spectrum of OI. This spurred the proposal for a new classification system to accommodate the long-standing functional and relevant grouping of OI types and the expanding genotypes (3). Within this new classification scheme (table 1), OI types I-IV retain their clinical descriptions and are associated with autosomal dominant mutations in the two collagen genes. Types V and XV OI are the only other newly discovered types to have an autosomal dominant inheritance pattern. The remaining OI types, typically occurring at much lower frequency, are autosomal recessive with OI type XVIII having an X-linked inheritance pattern.

Table 1.

Classification and Clinical Features of Osteogenesis Imperfecta

OI Type ¹	Clinical Features	Inheritance	Defective Gene/Protein
	Defects in collagen synthesis, structure, and assembly		

OI Type¹	Clinical Features	Inheritance	Defective Gene/Protein
I	Normal stature, little or no deformity, blue sclerae, hearing loss in 50% of families. Dentinogenesis imperfecta (DI), where present, is a highly heritable trait.	AD ²	COL1A1/Collagen I (α 1)
II	Lethal in the perinatal period; minimal calvarial mineralization with relative macrocephaly, beaded ribs, compressed femurs, marked long bone deformity, platyspondyly.	AD (new mutations)	COL1A1/Collagen I (α 1) or
III	Progressively deforming bones, usually with moderate deformity at birth. Relative macrocephaly. Scleral hue varies, often lightening with age. DI common, hearing loss common. Pectus deformities. Severe scoliosis. Stature very short. Mild to moderate bone deformity. Relative macrocephaly.	Parental mosaicism	COL1A2/Collagen I (α 2)
IV	Scleral hue may be bluish at birth, lightens with age. DI expression variable, associated with higher risk for basilar invagination. Scoliosis, short stature and osteoporosis expression and severity variable.	AD	COL1A1/Collagen I (α 1) or
V	Phenotypically indistinguishable from type IV OI. Distinctive histology (irregular arrangement or mesh-like appearance of lamellae). Also have triad of hypertrophic callus formation, dense metaphyseal bands, and ossification of the interosseous membranes of the forearm. Moderate to severe skeletal deformity. Variable scleral hue. Hearing loss and DI not observed. Distinctive histological and radiographical features include “fish-scale” appearance of bone under polarized light and excessive osteoids in childhood. Elevated alkaline phosphatase activity, also in childhood.	Parental mosaicism	COL1A2/Collagen I (α 2)
VI		AD	IFITM5/BRIL
VII		AR	SERPINF1/PEDF
VIII		AR	CRTAP/CRTAP

Defects in bone mineralization

Defects in collagen modification and processing

OI	Clinical Features	Inheritance	Defective Gene/Protein
Type 1	electrophoresis. Severe or lethal bone dysplasia similar to types II & III.		
VIII	Microcephaly. White sclerae. Rhizomelia. Severe osteoporosis. Collagen over-modification on gel electrophoresis. Moderate to lethal bone dysplasia similar to types IV or II OI.	AR	LEPRE1/P3H1
IX	White sclerae. No rhizomelia. Moderately severe osteoporosis in survivors. Severe bone dysplasia. Relative macrocephaly. Blue sclerae.	AR	PPIB/CyPB
X	Hearing loss not observed. Dentinogenesis Imperfecta. Pulmonary complications. Renal stones. Generalized hypotonia. Deforming dysplasia and kyphoscoliosis (both progressive). Grayish-white sclerae. Normal hearing. Ligamentous laxity, joint hyperextensibility. Coxa vara. Wormian bones, wedge	AR	SERPINH1/HSP47
XI	vertebrae. Elevated alkaline phosphatase. <i>Mutations in FKBP10 also cause Bruck Syndrome Type I (severe OI with congenital contractures) and Kuskokwim Syndrome (congenital contractures with osteopenia but no OI).</i> Moderate to severe. White sclerae. No hearing loss or DI.	AR	FKBP10/FKBP65
XII	Generalized hypotonia and bone deformity. Joint hyperextensibility. Possible long bone bowing. Wormian bones. High bone mass despite recurrent fractures and high turnover. No shortening of extremities.	AR	BMP1(mTLD)/BMP1
Defects in osteoblast differentiation			
XIII	Moderate bone dysplasia. White sclerae. Mixed hearing loss. Micrognathia. No DI. Wormian bones. Bowing of upper and lower limbs. Mild scoliosis. Mild pectus carinatum.	AR	SP7/Osterix
XIV	Generalized osteoporosis. Moderate bone dysplasia. Mild to moderate short stature in some. Mildly gray-blue sclerae. Generalized osteopenia. Bowing deformity. Thin ribs. Wormian bones. Cardiovascular	AR	TMEM38B/TRI C-B

OI Type ¹	Clinical Features	Inheritance	Defective Gene/Protein
	defects. Moderate to severe; progressively deforming. Bluish to blue sclerae in some. Marked deformity, bowing of long bones.		
XV	Striking scoliosis; vertebral fractures. Wormian bones. Generalized demineralization. Osteopenia. Muscle hypotonia. Some with neurological defects.	AR/AD	WNT1/WNT1
XVI	Severe. Blue-gray sclerae. Soft calvarial bones. Thin or beaded ribs. Multiple fractures neonatally and healing with deformity. Bowed femora and humeri. Easy bruising.	AR	CREB3L1/OASIS
XVII	Severe. White sclerae. No DI. Scoliosis. Joint hyperlaxity.	AR	SPARC/Osteonectin
XVIII	Severe. Sclerae blue or white. Pectus deformity. Scoliosis.	X-linked recessive	MBTPS2/S2P

1

Modified from Silience et al., 1979

2

AD = autosomal dominant; AR = autosomal recessive

Patients with type I OI have a distinctly milder form of the disease, which is generally not detectable at birth. Patients with type I OI tend to present with early osteoporosis; DEXA z-scores range from -1 to -3. Patients may have their first fracture in the pre-school years, for example when attaining ambulation. They may also have a series of fractures in the pre-pubertal years due to mild trauma. Fractures generally decrease dramatically in the post-pubertal years. Patients with type I OI have normally modeled bone and may have mild bowing of long bones and minimal central vertebral compressions. They are often a few inches shorter than same gender relatives. Leg length may be disproportionately short. Blue scleral hue is a defining feature in the Silience classification, though, in actuality, it may be present or absent. These patients are expected to be spontaneous ambulators, but may have some mild delay of gross motor skills. They can be expected to have a full life span, limited only by greater vulnerability to accidental trauma.

Type II OI is the perinatal lethal form. Infants may be stillborn; if they survive birth, they usually die in the first two months of life (4). Some infants with type II OI may live for as long as a year, but

eventually do succumb to multiple pneumonias or respiratory insufficiency. The limbs, especially the legs, are short with severe bowing deformities ([Figure 1](#)). Most often the legs are abducted into the classic “frog leg position”. The cranium is relatively large for the trunk and is very poorly ossified. The anterior fontanelle is large, and often extends frontally to the forehead and laterally along the sagittal suture. The posterior fontanelle is often open as well. The presence of two enlarged fontanelles frequently results in ossification only along the lateral plates and for a fingertip breadth at the crown. The infants tend to have flat triangular facies with a small beaked nose and dark blue-gray sclerae. The thorax is usually deformed with a narrow apex. Radiographic examination reveals multiple in utero fractures in various stages of healing. There may be beads of callus on the ribs, which are quite gracile. The long bones are very osteoporotic with minimal to no cortex. Upper extremity long bone morphology is better than that of the lower extremities. The lower long bones are crumpled as well as fractured and are abnormally modeled, with a cylindrical shape. Thus, the defect in type I collagen affects the development as well as the mineralization of the skeleton.

Figure 1.

Radiograph of infant with type II OI. Shows severe osteoporosis of skeleton with fractures of upper extremities, crumpled femora, flared rib cage with narrow apex and multiple beads of callus on each rib.

Type III OI, also known as the Progressive Deforming type ([1](#)), is the most severe form of OI compatible with survival beyond infancy and is severely disabling. Individuals with type III OI can have a full life span; however, a significant proportion succumb to respiratory or neurological complications, either during childhood or in early to middle adult years. The long bones of individuals with type III OI are soft as well as fragile and can have bowing deformities of 70-90°, caused either by the tension of normal muscle on the bone, or from angulated healing of fractures ([Figures 2, 3](#)). Long bones have a cylindrical shape with more modeling of the metaphysis than in type II; by late childhood there is often exaggerated metaphyseal flaring accompanied by a slender diaphysis ([5](#)). An additional finding in the metaphysis and epiphysis of lower limb long bones are so called “popcorn” calcifications caused by disorganization around the growth plate. More than half of the individuals with type III OI develop this radiographic change between the ages of 4 to 14 years with resolution of popcorn calcifications when epiphyses close ([6](#)). Fractures can occur from activities of daily living; there may be hundreds of fractures in a lifetime. DEXA z-scores are in the range of -5 to -7 SD. Body proportions are better preserved than in type II OI, with less shortening of the extremities relative to the

trunk. The calvarium is almost always relatively macrocephalic for the body and frequently measures greater than 95th centile for age, though occasionally children will have a normal or smaller than average head circumference for age. The midface is flat with frontal bossing and DI is common and its presence correlates with that of basilar invagination (7). Mixed type hearing loss occurs more commonly in adults than children with type III OI. Children with type III OI almost always develop chest wall abnormalities; pectus carinatum is more frequent and less detrimental to pulmonary status than pectus excavatum. Virtually all children with OI type III will also develop significant scoliosis. Even with aggressive intervention, these individuals are most often full-time wheelchair users.

Figure 2.

A, B: Radiographs of lower extremities of type III OI child. Shows osteoporosis, flared metaphyses, and placement of intramedullary Rush rod. C, D: Radiographs of child with type III OI. Shows lower long bones osteoporotic with cystic formation and “popcorn” metaphyses, and placement of telescoping intramedullary rods. Lateral view of spine shows anterior and central compression of multiple vertebrae.

Figure 3.

AP view of spine from type III OI child. Shows severe scoliosis and flared rib cage, as well as gracile and wavy ribs.

Type IV OI is the moderately severe type. The skeletons of these individuals are brittle, not soft. On average, people with type IV OI have dozens of fractures (Figure 4). Most fractures occur either prior to puberty or beyond middle age, with the intervening years relatively protected by sex steroids. Popcorn calcifications have been reported as a radiographic change associated with type IV OI; however, it does not occur as frequently as seen in type III (6). Individuals are significantly osteoporotic, with DEXA z-scores in the range of -3 to -5 SD. With medical intervention these individuals can expect to be community ambulators and have an essentially normal life span. Body proportions approach normal, although the legs are still short for the trunk and the cranium is relatively macrocephalic. As with type I OI, individuals with type IV are divided into types A and B by the Silience classification, based on the presence or absence of dentinogenesis imperfecta (8). Vertebral compressions in childhood and laxity of paraspinal muscles may lead to significant scoliosis.

Figure 4.

Radiographs of lower extremities of type IV OI child. Shows mild bowing and placement of Rush rod.
B: Lateral view of spine shows milder scoliosis and milder compression of vertebrae.

OI types V and above comprise the approximately 15-20% of individuals who have a phenotype characteristic of OI but who do not have a defect in the collagen genes *COL1A1* or *COL1A2*. In many ways, type V OI is clinically indistinguishable from type IV because both types present with frequent fractures, moderate deformity, ligamentous laxity, tendency to bruise easily and periodic fracture-related loss of mobility. Clinical, histological and molecular differences exist, however, that distinguish type V from IV. Individuals with type V do not have blue sclera or DI. In type V, the distinctive bone histology is an irregular arrangement or a mesh-like appearance of the lamellae. Patients also have a triad of hypertrophic callus, dense metaphyseal bands and ossification of the interosseous membranes of the forearm. This causes severely limited pronation/supination of forearms. In addition, the type I collagen protein of these patients has normal electrophoretic mobility (9). In 2012, it was found that all cases of type V OI are caused by the same recurring defect in the *IFITM5* gene that encodes the BRIL (Bone-restricted IFITM-like) protein, a known osteoblast marker which is highly expressed in mineralizing osteoblasts (10). The heterozygous mutation adds a 5-residue MALEP extension to the N-terminus of BRIL, disrupting the normal protein with a gain-of-function defect.

Type VI OI is clinically and histologically distinct from type V. Characteristics of individuals with type VI OI include short stature, ligamentous laxity, white or faintly blue sclera and no DI. There are no fractures or other signs of OI at birth. First fractures in type VI OI occur when affected individuals begin standing as infants/toddlers, with progressive deformity clinically similar to type III. Deformity caused by long bone fractures can be moderate to severe, often necessitating support devices for ambulation or wheelchairs to maintain mobility. Type VI OI is distinguished by distinct histologic and molecular criteria (11). Bone histology includes “fish-scale” pattern of the lamellae under polarized light, and decreased mineralized bone volume secondary to increased osteoid volume. This bone mineralization defect is a defining attribute of Type VI OI. Various autosomal recessive null mutations in the *SERPINF1* gene, which encodes PEDF (pigment epithelium-derived factor), a potent anti-angiogenic factor that binds to type I collagen and a tumor inhibitor, have been shown to cause OI type VI (12, 13). These patients have negligible serum PEDF levels, as opposed to type V and other types, in which PEDF serum levels are equivalent to controls. Individuals with a point mutation in one copy of the *IFITM5* gene, causing a p.S40L substitution in BRIL, present with histomorphologic and biochemical features of type VI OI, further underlining the connection between the two protein

products and OI types (14).

Molecular and biochemical defects in types VII, VIII and IX OI were the first of the recessive forms identified; specifically, each type has a defect which causes deficiency of one of the components of the collagen prolyl 3-hydroxylation complex. Although 3-hydroxylation of Pro986 in type I collagen had been known to occur for almost three decades (15), its importance to bone formation had not been appreciated. The initial understanding of recessive OI as being due to a deficiency of this ER-resident collagen modification complex shifted the paradigm for collagen-related bone dysplasias (16).

LEPRE1, *CRTAP* and *PPIB* are the three genes that encode the components of the collagen prolyl 3-hydroxylation complex, prolyl 3-hydroxylase 1 (P3H1- the enzymatic component of the complex), cartilage-associated protein (CRTAP- the helper-protein in the complex) and cyclophilin B (CypB), respectively. The proteins form a 1:1:1 complex in the endoplasmic reticulum (17). The complex binds collagen post-translationally and hydroxylates a single residue, Proline 986, on each $\alpha 1$ (I) chain. In normal collagen, over 90% of Pro986 residues are 3-hydroxylated. The importance of the collagen prolyl 3-hydroxylation complex for bone development became clear during investigation of the *Crtap* knock-out mouse. These mice have severe osteopenia, rhizomelia and later develop kyphosis. In addition, these mice lacked 3-hydroxylation of Proline 986 on both $\alpha 1$ (I) and $\alpha 1$ (II) collagen chains (18). The type I collagen of *CRTAP*- or *LEPRE1*-deficient individuals also lacks Pro986 hydroxylation. Surprisingly, this collagen is, in turn, overmodified by Prolyl 4-hydroxylase (P4H) and lysyl hydroxylases (LH), proteins that modify proline and lysine residues along the length of the helical region of both alpha chains. Excess modification of the helix indicates that folding of the helix has been delayed.

Interestingly, the phenotype as well as the collagen biochemical findings of *CRTAP* and *LEPRE1* null mutations are essentially indistinguishable. The basis of this similarity is the mutual protection of CRTAP and P3H1 in the modification complex (19). Cells with a null mutation in either gene are missing both proteins; restoration of the genetically deficient protein restores both proteins. Thus, null mutations in either gene cause absence of the complex from the cell.

Type VII OI is a lethal/severe recessive chondro-osseous dysplasia caused by null mutations in *CRTAP*. Fractures and limb deformities are present at birth. Radiographically, long bones are severely under-tubulated. Infants with type VII may develop respiratory insufficiency in the neonatal and postnatal periods and frequently die as a result of the underlying problem (i.e., pulmonary anatomical anomalies or infectious disease) (20). Distinctive features of type VII OI include small or normal head circumference, exophthalmia, white or light blue sclera, and rhizomelia. Deficiency of *CRTAP* affects

post-translational modification of both bone (type I collagen) and cartilage (type II collagen). The index pedigree from Quebec ([21](#)) first described for type VII OI has a hypomorphic defect in CRTAP ([18](#)) and a correspondingly milder phenotype with rhizomelia, coxa vara and white sclerae, more similar to dominant type IV OI in skeletal severity. These children have moderate growth deficiency. They attain ambulation without assistive devices.

Type VIII OI, caused by defects in *LEPRE1* (encoding P3H1) is also a severe/lethal autosomal recessive form of OI ([22-24](#)). Phenotypic characteristics overlap the dominant types II (lethal) and III (severe) OI, but have the distinguishing features of white sclerae, under-tubulated long bones and normal to small head circumference. Like type VII OI, rhizomelia is a distinctive feature of type VIII. Some individuals with type VIII OI have lived into their second or third decade (currently, the oldest known individual is mid-20's). Their physical exam is notable for extreme short stature, severe osteoporosis (DEXA z-scores of -6 or -7), and popcorn calcifications during the growing years. The most frequently identified *LEPRE1* mutation is a West African founder mutation (IVS5+2G>T) that also occurs in Afro-Caribbeans and African-Americans ([23](#)). Homozygosity for this West African allele has been lethal by 3 months of age.

Mutations causing deficiency of the third component of the collagen prolyl 3-hydroxylation complex, CyPB, are rarer and have been designated as type IX OI ([25, 26](#)). In this type, individuals have a distinctive phenotype compared to types VII/VIII in that they do not have rhizomelia. However, they share the white sclera of recessive OI. Total absence of cyclophilin B (CyPB) due to a mutation in the start codon causes moderately severe OI, overlapping dominant type IV OI in skeletal severity ([25](#)). Their osteoporosis is also moderately severe, with DEXA z-scores in the -2 to -3 range. They have attained community ambulation after osteotomy procedures. They have moderate short stature and may or may not have vertebral compressions. Biochemically, they have normal 3-hydroxylation of Pro986, consistent with persistence of the CRTAP/P3H1 complex in the absence of CyPB. More surprisingly, they do not have excess modification of their collagen helix, suggesting that CyPB is not the unique peptidyl-prolyl isomerase. In other cases, the presence of truncated CyPB ([26](#)) interferes with function of the 3-hydroxylation complex and causes severe or lethal OI. As for types VII and VIII OI, these CyPB mutations are associated with decreased Pro986 hydroxylation and delayed collagen folding.

Type X OI has been traced to a defect in *SERPINH1*, which encodes HSP47, a critical player in correct intracellular folding and transport of the procollagen triple helix. The only known *SERPINH1* mutation causing bone dysplasia in humans caused severe, progressive OI with a myriad of clinical signs, some common and some unusual for OI ([27](#)). This patient survived for 3 years (probably due to functionality

of the small amount of residual protein) despite the embryonic lethality of the null mutation in mice.

Type XI OI is caused by mutations in the *FKBP10* gene, which encodes a known PPIase, FKBP65 (28), another important protein for proper folding of procollagen molecules. The first discovery of *FKBP10* mutations was in a moderately severe type of OI (29). *FKBP10* mutations have since been shown to be causative in the recessive Bruck syndrome I (severe OI with congenital contractures) (30), and the contractures are now understood to be variable expression of the null *FKBP10* allele. Also, an in-frame tyrosine deletion in a PPIase domain of FKBP65 (31) was delineated as the cause of Kuskokwim syndrome, an Alaskan Yup'ik Eskimo congenital contracture syndrome with minor skeletal symptoms. Prior to these discoveries, there had been no known link between these three disorders, which represent the phenotypic range of the gene spectrum, encompassing bone dysplasia and congenital contractures of large joints.

Type XII OI is associated with an autosomal recessive inheritance pattern of mutations in *BMP1*, which encodes the C-propeptidase of type I procollagen (32). Individuals with type XII OI experience recurrent fractures early and, unlike previous OI types, have increased bone mineral density. A high bone mass OI phenotype was also observed in individuals with dominantly inherited mutations at the C-propeptide cleavage site of collagen (33). Conversely, mutations in the N-propeptidase ADAMTS-2, or the N-propeptide cleavage site, the N-anchor domain of the helical region cause combined osteogenesis imperfecta and Ehlers–Danlos syndrome (EDS) (OI/EDS) (34).

The subsequent, more recently identified, OI types are very rare, each with only a few cases described. Causative mutations reside in genes involved in regulation of osteoblast differentiation. Inheritance pattern is autosomal recessive for all except type XVIII OI, which is X-linked.

Type XIII OI has been described in two families with skeletal phenotype similar to that seen in Type IV OI (35, 36). The first report was on an Egyptian male, the second on an Iraqi sibship. Both families reported consanguinity. The associated gene is *SP7/Osterix (OSX)*, which is a transcriptional factor and a regulator of bone function in mouse models and in the human cases (35, 36).

Type XIV OI is caused by null mutations in *TMEM38B*, encoding TRIC-B, a cation channel also involved in cell differentiation. The mechanism for this disruption involves impaired osteoblast Ca²⁺ flux from cytoplasm into the ER. Reported cases were first identified among Saudi Arabian and Israeli Bedouins (37, 38), but have since been identified in individuals of other ethnicities (39). Their clinical phenotype is similar to that of Type IV OI, with distinctive histological features of decreased osteoblast number and normal mineralization at the tissue level, in contrast to the elevated mineral content seen in

other OI types. Because of the intracellular Ca²⁺ signaling involvement, cardiac involvement may occur at a higher frequency (39).

Type XV OI has been associated with mutations in *WNT1*, and reported in individuals of various ethnic backgrounds (40-43). Individuals with homozygous or compound heterozygous mutations in *WNT1* have Type IV OI phenotype, while those with heterozygous mutation in *WNT1* have osteoporosis (42). In its role as a stimulator of bone formation, WNT1 interacts with LRP5, which is known to cause a juvenile osteoporosis similar to type IV OI (44). Brain malformations have been reported in some individuals with this OI type.

Type XVI OI has a severity similar to that of Type II OI, in that almost all individuals diagnosed with it have died *in utero* (45). A living 11-yo male with Type XVI OI has severe bone dysplasia similar to that seen in Type III OI (46). Mutations in *CREB3L1*, encoding OASIS, an ER-stress transducer and regulator of genes in cellular differentiation and maturation, are causative (45). Mice lacking *Creb3l1* show spontaneous fractures due to severe osteopenia (47). Individuals with heterozygous mutations in *CREB3L1* have been reported to have features of blue sclerae, osteopenia, and mild recurrent fractures history (48).

Type XVII OI is caused by mutations in *SPARC*, whose protein product is a chaperone for extracellular matrix proteins. Only two individuals have been identified with this OI type (49). The presentation is similar to Type IV OI, with progressive skeletal involvement, including the spine.

Type XVIII OI has been described in male individuals from two families with phenotypes in the severity range of types III and IV OI (50). The gene involved, *MBTPS2*, codes for S2P, an intramembrane protease in the Golgi apparatus. In concert with S1P, S2P processes and activates transcription factors such as OASIS in the Regulatory Intramembrane Proteolysis (RIP) pathway. Despite the OASIS link, the phenotype for type XVIII is not as severe as that in type XVI. Obligate female carriers of *MBTPS2* mutations do not have OI features (50).

SECONDARY FEATURES OF OI

Growth

Short stature is the most prevalent secondary feature of OI. Children with types III and IV OI fall off normal growth curves by one year of age, entering a phase with slow growth that lasts until age 4-5 years. After age five years, children with type III OI have increased growth rates, but the slope is

always less than that of the normal curve. Average final adult stature is in the range of a 5-7-year-old for both sexes (51, 52). Children with type IV OI often grow either parallel to the normal growth curve or with a moderately decreased slope. However, they cannot make up for the loss of height incurred during the plateau phase, so average final stature approximates that of a 7-8 year old for females and a preteenager for males (51). OI types (III or IV) and sex are more correlative and predictive of stature growth than genotype (i.e. mutations in *COL1A1* or *COL1A2*) (51). Individuals with type I OI grow parallel to the normal growth curve and final height is usually a few inches shorter than same sex relatives (53). Growth pattern for individuals with the more rare OI types may mirror those for type I, III or IV as is the case for type V OI (9, 53). The cause of short stature in OI is not clear. Defects in primary development of long bones and their healing following repeated fractures, intraosseous calcifications at the growth plates, unequal opposition to musculature forces on soft bones, and scoliosis are all likely contributory.

Obesity or higher body mass index (BMI) is a prevalent finding in individuals with OI (51, 53). Type III OI and female sex are associated with BMI values significantly higher than those in the average pediatric population (51). While it is tempting to attribute this finding entirely to decreased mobility and activity, this has not been proven and other causes such as plasticity of osteoblast-adipocyte differentiation need to be explored.

Scleral Hue

Scleral hue is a defining feature of the Sillence classification, with blue sclerae in type I OI, white sclerae in type IV. This resulted in grouping children with inconsistent skeletal features. We consider scleral hue a secondary, not a defining, feature. Most people with type I OI have blue sclerae, but some will have white sclerae. Many persons with types III and IV OI will have blue sclerae. Blue sclerae have also been reported in at least some individuals in most OI types. Individuals with types VII and VIII OI have predominantly white sclerae.

The bluish tinge may result from decreased scleral thickness (54). However, it can also occur with normal thickness. In this case, tissues with different proteoglycan compositions, and therefore different hydration, may cause the blue tinge by their reflection of wavelengths of color.

Hearing Loss

A majority of adults with osteogenesis imperfecta have functionally significant hearing loss related to

combined conductive and sensorineural deficits (55). Molecular studies have revealed that hearing loss is not related to OI types or to location of mutation in *COL1A1* or *COL1A2* (56). In most cases, deficits are detectable only on audiology examination in childhood and the teen years; functional loss does not occur until the twenties. A study of hearing in Finnish children with OI reported loss greater than 20 dB in 6.7% (57); this is comparable to the 7.7% detected in the NIH pediatric OI population (58). Most pediatric hearing loss is first detected between ages 5-9 years; some children may require hearing aids.

For adults, the hearing deficits are very similar to those found in otosclerosis. Swinnen reported hearing loss in 97 of 184 patients, with the percentage of hearing-impaired patients (primarily bilateral, symmetric and progressive loss) increasing with age (59). There was significant variability in hearing pattern, even for identical mutations. Of 56 adult OI patients (60), those with conductive/mixed hearing loss had lower trabecular BMD relative to those with normal hearing or sensorineural loss. Possibly, OI patients with lower BMD might be more prone to microfractures, thinning of the ossicles and impaired bone remodeling in the temporal bone causing conductive hearing loss.

When hearing loss exceeds the compensation of hearing aids, surgical interventions may be used. Stapedectomy can give satisfactory long-term results; however, this surgery should not be undertaken routinely. The fragility of the small bones of the ear results in a significant percentage of unsatisfactory long term hearing restoration (61). However, stapes surgery in experienced hands often successfully resolves the conductive hearing loss in OI patients. Stapedotomy improves hearing and facilitates rehabilitation with a hearing aid. While OI genotype is not determinative of middle ear pathology, postoperative hearing gain in patients with OI types I and IV are identical (62). Given the rarity of OI and surgical complications in OI (i.e., middle ear anatomic anomalies and tendency for profuse bleeding), surgical outcomes may be better at medical facilities experienced with stapes surgery and hearing loss due to OI (63). Insertion of cochlear implants has been reported in a few case studies (64); however, this data is limited. The implants have resulted in a short-term improvement in hearing ability, but long term hearing restoration remains unknown (65).

Cardiopulmonary Complications

Cardiopulmonary complications of OI are the major cause of mortality directly related to the disorder (66). Infants with type II OI die of respiratory insufficiency or pneumonias. Children with type III OI develop vertebral collapse and kyphoscoliosis, which contribute to restrictive lung disease. These skeletal features, as well as the inactivity associated with wheelchair mobility, predispose them to multiple pneumonias. Lung disease may progress to *cor pulmonale* in middle age. Pulmonary function

should be evaluated every few years, starting in childhood, to facilitate early management with bronchodilators, and should be correlated with arm span rather than reduced stature. The need for chronic oxygen may arise as early as adolescence but most frequently occurs in the forties and fifties. Pulmonary dysfunction was not correlated with kyphosis or chest wall deformity (67).

Pulmonary compromise is strongly correlated with thoracic scoliosis of more than 60 degrees (67). In addition, sternal deformities such as pectus carinatum that frequently occur in severe type III OI, alter respiratory muscle coordination and ventilation (68). In addition to these external forces on respiration, there are the intrinsic factors that result from mutant collagen composition in OI. A longitudinal pediatric OI cohort with collagen structural mutations but without scoliosis was shown to have significant decline in PFTs (tidal lung capacity and FVC) during childhood, albeit with a slower rate of decline than children with scoliosis (69). Type I OI causes no aberrant cardiopulmonary function at rest (69).

Murine and patient data also point to direct effects of OI on the cardiac system, in addition to the *cor pulmonale* that is a late secondary effect of pulmonary dysfunction. This is not surprising given that type I collagen accounts for 75% of total collagen in the myocardium. In children with moderate to severe OI, the abnormality most frequently noted is mild regurgitation of the tricuspid valve (69). In adults, dilatation of the aorta and pulmonary vessels (70) and regurgitation of the mitral and aortic valves (66) are the most frequently reported findings. Adults with OI should have regular monitoring of blood pressure, since elevated BP, age and OI were significant predictors of increased LV mass (71). In addition, adults with type III OI had greater RV dimensions (72). Valvular and aortic surgery carry higher risk in OI but pose fewer problems than in Marfan syndrome (73).

Neurological Complications

Osteogenesis imperfecta is frequently associated with either relative or absolute macrocephaly. Between ages 2-3 years, the child's head circumference may rapidly cross centile lines for age. Prominence of sulci and ventriculomegaly are not associated with intellectual deficit. There is a high frequency of basilar invagination (BI) in patients with severe osteogenesis imperfecta. BI generally progresses slowly in childhood; radiologic evidence for BI may be present for years before symptoms are present. Children should be screened by CT every 2-3 years, and followed annually by MRI if radiographic signs of BI develop.

In a longitudinal study on craniocervical junction in growing OI patients (74), almost half of patients

with a skull base abnormality had comorbidities of BI, basilar impression and platybasia. A small study based on lateral skull radiographs found skull base abnormalities in about a fifth of the studied OI patients, with platybasia being the most frequent finding. Stature (Z -score $< -3SD$) conferred the highest risk of developing skull base abnormalities. Bisphosphonate treatment was not protective against skull base abnormalities ([75](#), [76](#)).

Early intervention with occipitocervical bracing has been recommended, along with shunting of hydrocephalus, to slow the adolescent progression of significant basilar impression ([77](#)). Severe cases will still require neurosurgery. Without surgery, immobilization might result, which leads to atrophy of the muscles from disuse, and ankylosis of the joints ([78](#)).

Favorable outcomes have been obtained by surgical intervention delayed until the patient experiences severe headaches as well as long tract signs. Typical clinical features of BI include headaches, nystagmus, dysphagia, ataxia and changes in facial sensation that, if not treated, can progress to rapid neurologic decline and/or respiratory distress ([79](#)). As patients become symptomatic they should be followed in centers (University of Iowa, Johns Hopkins) with experience in performing anterior ventral decompression with occipitocervical fusion in OI patients ([77](#), [80](#)).

DIAGNOSTIC WORK-UP AND DIFFERENTIAL DIAGNOSIS

Crucial elements of the diagnostic work-up focus on the skeletal system. The physical exam includes measurements of length and head circumference, as well as notations on body proportions, including upper segment: lower segment ratio and arm span. In addition, the segmental lengths of each limb are measured to detect asymmetry. Individuals with OI frequently have relatively long arm span for length and a shortened lower segment (pubis to floor). Sclerae may be blue or blue-gray and teeth may have dentinogenesis imperfecta, with opalescent or yellow-brown enamel. In the thorax, the spine should be examined for scoliosis and the rib cage for flare and/or pectus carinatum or excavatum. In an infant, the size of the fontanelles should be noted. Also essential is a careful family pedigree, with inquiries about fractures, hearing loss, dentinogenesis imperfecta, adult height, racial background and consanguinity.

Radiographic examination consists of a selective skeletal survey. AP and lateral views of the long bones are examined for significant osteoporosis, bowing, healing fractures, metaphyseal flare and the sharpness of the growth plate. AP and lateral views of the spine are examined for scoliosis, vertebral compressions, and sharpness of the vertebral endplates. Rhizomelia is suggestive of recessive types of OI, although it occurs more commonly in chondrodystrophies. A lateral view of the skull should also be

obtained to detect Wormian bones.

It is essential to obtain a DEXA of the lumbar vertebral bodies for a relatively quantitative assessment of the individual's osteoporosis. Since the bone matrix in types II-IV, VII-XII OI is qualitatively abnormal, the DEXA z-score reflects the structural arrangement of the mineral as well as the quantity and therefore is not a straightforward quantitative measurement.

Differential diagnosis varies with the severity of OI and age of the patient. On prenatal ultrasound, severe OI may be confused with thanatophoric dysplasia, achondrogenesis type I, or campomelic dysplasia, all of which demonstrate relatively large heads and short limbs. Type III OI may need to be distinguished from infantile hypophosphatasia, which presents with severe osteoporosis and micromelia. Hypophosphatasia results in low serum alkaline phosphatase and increased inorganic pyrophosphate, while in OI, serum alkaline phosphatase is normal or increased. Type IV and more severe type I OI may be confused with primary juvenile osteoporosis or other secondary causes of osteoporosis in childhood, such as hypogonadism or malignancy. The major differential diagnosis with types I and IV OI is non-accidental trauma.

Molecular genetic sequencing, whether via broad-based panels or step-wise testing, has become the common first approach to diagnosis. Step-wise genetic testing applies in areas where access and cost remain challenging, and would include interrogating dominant OI genes first in individuals without family history of OI. This approach would yield informative findings in ~80% of the cases, and if a causal mutation is not identified may be followed by sequencing of recessive OI genes. Biochemical studies of collagen and of the components of the collagen prolyl 3-hydroxylation complex can complement decreased BMD and other skeletal features of OI, in cases of uncertain molecular findings.

COLLAGEN MUTATIONS AND GENOTYPE-PHENOTYPE CORRELATION

The majority (85-90%) of OI causing mutations occur in the genes that code for the two chains that comprise type I collagen, the major protein of the extracellular matrix of bone, skin and tendon ([81](#)). Type I collagen is a heterotrimer composed of two copies of the $\alpha 1$ chain, encoded by the *COL1A1* gene on chromosome 17, and one copy of the $\alpha 2$ chain, encoded by *COL1A2* on chromosome 7. The two alpha chains are similar in sequence organization; they are composed of 338 uninterrupted repeats of the sequence Gly-X-Y, where Gly is glycine, X is often proline and Y is often hydroxyproline. A glycine residue in every third position along the chain is crucial for helix formation; the small size of

glycine's side chain allows it to be tucked into the sterically constricted internal aspect of the helix. The collagen genes are organized with each exon coding for the helical region beginning with a glycine codon and ending with a Y-position codon; therefore the skipping of a helical exon does not cause a frameshift in the collagen transcript.

As of 2019, over 1600 unique pathogenic variants in both chains of type I collagen had been described in OI patients (82-84). One general correlation between genotype and phenotype emerged: Type I OI, the mild form, is caused by quantitative defects in collagen. Only half the normal amount of collagen is produced but all the collagen produced is structurally normal. This is almost always due to a null allele of *COL1A1* (85). On the other hand, types II, III and IV OI, the clinically significant forms, are caused by structural defects in either of the type I collagen chains. About 80% of these structural mutations cause the substitution of another amino acid, with a charged, polar or bulky side chain, for one of the obligatory glycine residues occurring in every third position along the chain. Glycine substitution mutations temporarily block helix formation and cause over-modification (glycosylation) of the chains of the trimer. About 20% of structural mutations are single exon skipping defects, which are incorporated into the trimer because the frame of the transcript remains intact (84). Essentially all of the collagen mutations are dominant negative mutations. They exert their effects by being secreted and incorporate into the matrix, causing a weakened higher order structure.

For structural mutations of type I collagen, the relationship between genotype and phenotype has been elusive. A lethal mutation was found to be more likely in the $\alpha 1$ chain, in which about one-third of known glycine substitutions caused lethal OI, than in the $\alpha 2$ chain, in which only ~20% were lethal (84). Nonetheless, both chains contain substantial numbers of mutations causing the full range of the OI phenotype. The two chains have different patterns of lethal and non-lethal mutations along the helical region, supporting different roles for the two chains in matrix. Lethal and non-lethal clusters alternate along the $\alpha 2$ (I) chain (86). The clusters are quite evenly spaced, and appear to play a role in regularly repeating interactions of collagen with non-collagenous matrix molecules. When the alignment of cluster boundaries was compared to the clinical outcome of mutations, the cluster boundaries correctly predicted the phenotype of 86% of $\alpha 2$ (I) mutations (84). In the $\alpha 1$ (I) chain, the mutations may disrupt the stability of the collagen helix itself (84). Two regions of uninterrupted lethal mutations in the carboxyl end of $\alpha 1$ (I) coincide with the major ligand binding region (MLBR) for integrins, fibronectin, and COMP (84).

The phenotype-genotype relationship in OI is complicated by multiple examples of variable expression. Individuals with the same genotype have a different phenotype, an interesting feature of many

dominant disorders. In the $\alpha 1(I)$ chain, there are several dozen sites with examples of extreme variable expression of the same mutation; these glycine substitutions are found in both lethal and non-lethal forms of OI. A more frequent occurrence in both chains is substantial variation in severity between family members or unrelated individuals with the same mutation. For example, phenotype can range from type III to IV OI. One explanation for this interesting feature may be the existence of discrete modifying genes. Understanding modifying factors may provide new approaches to treatment.

Animal models for OI, including the *Brtl* (brittle), Amish, and *Aga2* (abnormal gait 2) mice have shed new light on pathophysiology, modifying factors and treatment of OI. The *Brtl* mouse is a knock-in model for type IV OI (87). It contains a classic glycine substitution in one allele at $\alpha 1(I)$ G349C, which causes dominant negative OI. The *Brtl* mouse reproduces the phenotype, histology, biochemistry and biomechanics of the disorder. It also has variable phenotypic expression, which may lead to an understanding of modifying factors. Clinically relevant findings elucidated with the *Brtl* mouse model include post-pubertal improvement in bone matrix material properties (88), the imbalance between decreased osteoblast function and increased osteoclasts precursors as a potential lead to novel OI therapies (89), and the concomitant beneficial and detrimental effects of cumulative bisphosphonates exposure (90). A knock-in mouse model for the $\alpha 2(I)$ chain has also been published (91). It recapitulates the mutation found in a large Amish pedigree that causes a Gly610Cys substitution, hence its designation as the Amish mouse. Long bones of the Amish mouse are less fragile than those of *Brtl*. The human pedigree with the Gly610Cys substitution has a wide range of phenotypic variability. Crossing the murine mutations into different genetic backgrounds demonstrated that whole bone fracture susceptibility was influenced by factors reflected in the size and shape of bone, and will be useful for the identification of genetic modifiers. Finally, the *Aga2* mouse has a dominant mutation located in the terminal C-propeptide that was created using an N-ethyl-N-nitrosourea mutagenesis strategy (92). Like the *Brtl* mouse model, the *Aga2* phenotype has a perinatal lethal and a severe surviving form. This mouse will provide important insight into the special mechanism of OI caused by mutations in the C-propeptide. Since the C-propeptide is normally removed before collagen is incorporated into matrix, it is not clear why mutations in this region should cause moderate to lethal OI. In *Aga2* osteoblasts, the intracellular retention of abnormal collagen chains has been shown to induce the Unfolded Protein Response (UPR) and result in cellular apoptosis.

In addition, there is a naturally occurring mouse model for type III OI, the *oim* mouse (93). Although this mouse has been extensively studied, its histomorphometry differs from that seen in classical dominant OI, limiting the utility of this model (94). The *oim* mouse is also atypical in other ways. First,

although it has a collagen defect in *COL1A2*, the phenotype is recessively inherited vs the dominant inheritance of other type I collagen defects. Second, the collagen chain configuration in oim does not normally occur in bone. The defect in oim in the $\alpha 2(I)$ chain prevents the fully synthesized chain from incorporating into heterotrimer and leads to the production of an $\alpha 1(I)$ homotrimer. Third, and perhaps most importantly, the mechanism of bone defect in oim is also atypical. Patients with $\alpha 1(I)$ homotrimer caused by null-mutations in the amino end of the $\alpha 2(I)$ chain have been shown to have Ehlers/Danlos Syndrome but not OI (95, 96). Since the bone dysplasia of oim cannot be directly attributed to the presence of homotrimer, but is likely connected to the cellular effects of degrading unincorporated $\alpha 2(I)$ chains, it is impossible to meaningfully interpret oim investigations.

Murine models for types V-XII, XV, and XVII have been developed (97, 98). Canine models for types III and X, and zebrafish models for types I-IV, VII, VIII, and XIII have also been reported (98, Forlino *A et al., Matrix Biology, In Press*).

GENETIC COUNSELING AND RATIONALE FOR COLLAGEN STUDIES

Genetic counseling is an essential component of complete care for individuals who have OI. More than half of individuals with autosomal dominant OI have a family history of OI. In a Finnish survey (57), about 65 percent of individuals with OI were in families in which a prior generation was affected and the remaining 35 percent represented new mutations in a type 1 collagen gene. In contrast, individuals with autosomal recessive OI seldom have a family history. Collagen studies are useful in cases where the molecular sequencing result is equivocal. Virtually all type I collagen mutations have dominant inheritance. If no collagen mutation is identified, abnormal collagen biochemistry can point to defects in *CRTAP* or *LEPRE1*. *PPIB* defects will rely on sequencing for detection, since collagen biochemistry may be normal or abnormal.

In autosomal dominant OI, a severe presentation is likely to be the result of a spontaneous mutation that occurred at or around conception; the affected individual is likely to be the first affected person in the family. The parents of a child with a *de novo* mutation are at no increased risk of recurrence compared to the general population. However, genetic testing of both child and parents is required to determine whether the OI is inherited from a mosaic parent (see below), which occurs in 5-10% of new cases and increases the risk of recurrence. Individuals who are affected with dominant OI have a 50% risk of transmission with each pregnancy.

Genetic counseling for autosomal recessive OI is challenging given the limited carrier information about these newly identified OI types. Certainly, parental consanguinity increases the risk that a child may have recessive OI. However, data have shown that the carrier frequency for type VIII OI among contemporary West Africans is over 1%; among African Americans about 1/200-300 individuals are carriers (99). Currently the carrier frequency of other recessive OI types is not known. Because recessive OI types can present as lethal OI and be incorrectly assumed to be type II OI, the genes for type I collagen frequently are not sequenced leading to the missed diagnosis of recessive OI and parental carrier status. The parents of a child with recessive OI have a 25% risk of recurrence. The mother of a son with X-linked OI overall has a 25% risk of recurrence with an unaffected partner.

Parental Mosaicism

In some families, clinically unaffected parents will have more than one child with dominant OI. This occurs because one parent is a mosaic carrier of the mutation. Presumably, the mutation occurred during the parent's fetal development; that parent then has both a normal and a mutant cell population. The proportion of mutant cells and their distribution in somatic and germline tissues depends on the timing of the mutation and the distribution of cells arising from the first mutant cell (100). The frequency of occurrence of mosaic parents is relatively high in OI. Empirically, 5-10% of unaffected couples whose child has dominant OI will be at risk of recurrence. For those couples in which one member is a mosaic carrier the recurrence risk may be as high as 50%, equivalent to the fully heterozygous state. To date, all mosaic parents have been detectable by examination of leukocyte DNA for the mutation present in their child. The mutation may also be detectable in dermal fibroblasts, hair bulb and germ cells.

PRENATAL DIAGNOSIS

For the first case of moderate to severe OI in a family, prenatal diagnosis will probably occur during ultrasound at 18 to 24 weeks' gestation (101, 102). Given the severity of types VII-IX, XIV-XVI and XVIII OI and their clinical overlap with types II and III OI, the first case of recessive OI in a pedigree can be expected to be diagnosed in the same timeframe by ultrasound.

Detecting recurrence of all OI types prenatally is easiest if the exact mutation in the affected child is known. In that case, a potential mutation in the current pregnancy can be detected early and with confidence. Cultured chorionic villi cells (CVS) can be used for DNA or RNA extraction and detection

by either PCR and restriction enzyme digestion or sequencing. CVS can also be used for biochemical analysis if the known mutation causes significant collagen protein over-modification ([100](#)).

Amniocentesis is only appropriate for molecular diagnosis via RNA or DNA analysis. Biochemical analysis of amniocytes is complicated by the overproduction of $\alpha 1(I)$ chains; the excess chains form homotrimers, which are overmodified and co-migrate with overmodified heterotrimers, potentially causing a false-positive test result ([100](#)). At this time, there are no data available on expression of the components of the 3-hydroxylation complex in CVS or amniocytes. Thus, analysis of DNA by sequencing or restriction digestion will be required.

Collagen analysis is useful when the diagnosis is equivocal. A positive collagen biochemical study can counteract charges of child abuse in mild cases, although the absence of a positive study still leaves a substantial possibility (about 25%) of a false negative result. False negative biochemical tests occur with most mutations in the amino-quarter of the alpha chains, which is also a region where almost all mutations are non-lethal ([103](#)). A positive collagen analysis can also settle subtle distinctions between type IV OI and idiopathic juvenile osteoporosis.

From a research standpoint, each new collagen mutation delineated in OI provides information about genotype-phenotype relationships either directly or by making the cells containing that particular mutation available for studies of mechanism at the level of bone matrix. Further, mutations may vary in response to different therapeutic approaches. Determination of mutations that cause OI may allow investigators to understand which drugs or therapies will be helpful for different individuals.

THERAPEUTIC APPROACHES

A multidisciplinary approach to OI management is most beneficial ([104](#)). A combination of nonsurgical treatment (e.g. rehabilitation, bracing, splinting), surgical intervention, and pharmacological management (bisphosphonates or growth hormones) are used.

Conventional

Conventional management of OI involves intensive physical rehabilitation, supplemented with orthopedic intervention as needed. Many parents and physicians place undue importance on the number of fractures sustained by children with OI. Fracture number may not be as important in judging the severity of the disorder as the degree of trauma needed to cause a fracture. In general, children with type III OI sustain fractures from more trivial trauma than those with type IV OI. In addition, they tend

to have more fractures in arms and ribs than occur in type IV. Fractures, in addition to long bone deformity, can lead to significant physical handicap.

The goal of physical rehabilitation for children with OI is to promote and maintain optimal functioning in all aspects of life. This is best accomplished by a program combining early intervention, muscle strengthening, and aerobic conditioning. Early intervention should include correct positioning of the infant. Proper head support to help avoid torticollis and neutral alignment of the femora are essential (105). Custom molded seats can help with lower extremity alignment as well as head and spine positioning (105). Gross motor skills are delayed in OI, mostly because of muscle weakness. This can be addressed with isotonic strengthening exercises of the deltoids and biceps in the upper extremity and the gluteus maximus and medius and trunk extensors in the lower extremity. Strengthening of these muscle groups will ensure that children are able to lift their limbs against gravity and transfer independently (106).

Physical therapy should be directed by a therapist experienced with OI, using an individualized program to maximize the BAMF (Brief Assessment of Motor Function) and muscle strength scores. Children and adults with severe forms of OI will have the challenge of gaining motor skills and then having to regain them after fractures, even with the placement of intramedullary rods and current pharmacotherapy. Pain and weakness must be managed in parallel with fear of re-fracture. Water therapy is often a useful adjunct, allowing partial weight bearing as activity is regained. Young adults with severe OI reported lower levels of activity, employment and transportation use, though many severely affected young adults have gone independently to college with facilitation by an aide and live employed, independent lives. Hence there are occupational therapy challenges beyond physical therapy for facilitation of full lives for young adults.

Children with mild type I OI can be differentiated from other OI children, have generally normal motor activity and are independent for self-care. Many children with mild disease have the musculoskeletal ability to play non-contact sports. For these children, the strength and functionality of the ankle plantar-flexor group is critical for jumping, hopping and maneuvering, and strengthening these muscles can be a high-yield goal. Joint hyperextensibility may hamper movement in these children and should be addressed.

In patients with potential, protected ambulation should be initiated as early as possible. This frequently requires a combination of surgical correction and physical therapy. Individuals with OI should be under the care of an orthopedic surgeon with experience in the management of this disorder. Fractures should

be evaluated with standard x-rays and should be managed with reduction and realignment, as needed, to prevent loss of function. Cast immobilization should be monitored to minimize any worsening of osteoporosis and muscle weakness. The decision to intervene surgically must take into account functional as well as skeletal status. Appropriate goals for surgery are to correct bowing to enhance ambulation potential and to interrupt a cycle of fracturing and refracturing. The classical surgical procedure was developed by Sofield and Millar, with multiple osteotomies, realignment of the long bone sections and fixation with intramedullary rods. Indications for this procedure include long bone angulation of greater than 40°, functional valgus or varus deformity which interferes with gait, or more than two fractures in the same bone in a 6-month period. Both elongating [Bailey-Dubow (BD) and Fassier-Duval (FD)] and non-elongating (Rush) rods are currently used for intramedullary fixation. Elongating rods have the advantage of extension with growth, but have a high rate of migration from OI bone (107). A recent study found proximal migration in 7 of 50 postoperative femora studied (108). The risk of proximal rod migration was decreased by correcting angular deformity and securing the rod at the distal physis. The possibility of migration needs special attention at follow-up, since it is still significant with FD as well as BD rods. The complication rate is similar for the two types of extensible rods, so choice of rod is best based on surgical experience and preference (109). Initial FD femoral rodding improved ambulation, self-care and gross motor skills (including mobility) in children with OI with significant femoral deformities beyond physiological expectations (110). Rush rods have less migration potential but need revision as the child outgrows them. In general, intramedullary rods induce significant cortical atrophy through mechanical unloading, especially in the diaphysis. The least stiff and smallest diameter rod possible should be utilized. Current intramedullary rodding procedures necessitate smaller incisions and, therefore, reduce pain and improve healing time after surgery.

Rarely, long-leg bracing may be indicated to provide support for weak muscles, control joint alignment and improve upright balance. Stabilizing the pelvic girdle and controlling the knees helps facilitate independent movement. Braces do not provide protection per se against fractures. Instead, bracing support promotes increased independent activity that may actually put the child at risk of incurring additional fractures. However, the advantages of increased independence and higher functional level tend to outweigh any increased fracture risk.

Due to an increasing lifespan in OI patients, clinicians may see increased incidence of OI hip osteoarthritis. In a series of patients with OI undergoing total hip arthroplasty with a median follow-up of 7.6 years (4 to 35 years), the survival rate of the primary total hip arthroplasty was 16% and there were ten complications: fractures, septic loosening and aseptic loosening (111). Preoperative planning,

because of altered patient anatomy, should involve a custom appliance fabricated based on the patient's CT scan to improve the long-term outcome.

Significant scoliosis is a feature of most type III and some type IV OI. Severe scoliosis does not correlate with number of collapsed vertebrae, because ligamentous laxity is a strong contributing factor. Since resultant thoracic deformities can lead to pulmonary compromise, routine attention to the OI spine is warranted (7). Scoliosis in OI does not respond to management with Milwaukee bracing. Spinal fusion with Harrington rod placement can provide stabilization and some correction to prevent pulmonary complications, but will not fully correct the curve. For best results, corrective surgery should occur when the curvature is less than 60°. In a study of 316 patients with OI, 157 (50%) had scoliosis (39% for type I, 54% for type IV, and 68% for type III) (112). Scoliosis surgery utilizing hooks and wire systems produce many complications in OI (113). Novel methods utilizing pedicle screw fixation systems have unique biomechanical advantages; long term effectiveness remains to be determined.

Pharmacological Therapy

When bisphosphonate treatment was introduced in the 1990's, it caused great excitement in the OI patient community and generated a rush to treatment. These drugs are synthetic analogs of pyrophosphate; their mechanism of action involves the inhibition of bone resorption. Bisphosphonates are deposited on the bone surface and are ingested by osteoclasts, inducing apoptosis. Because they inhibit bone resorption, these drugs have been used to treat malignancies with bony metastases, most commonly breast cancer. In the oncology context, their ability to attenuate the need for major pain medications has been noted, although the duration of this effect was limited in controlled trials. There is also extensive experience with these compounds in treatment of post-menopausal osteoporosis. Only limited knowledge about treatment of patients with structurally abnormal bone matrix had been gathered, and they had not previously been used to treat children.

When used in patients with OI, bisphosphonates would presumably not affect the deposition of abnormal collagen into matrix. Thus, patients might have quantitatively more bone after treatment, but it would not be more structurally normal than before drug administration. Uncontrolled studies of pamidronate use in children, teenagers and infants with OI reported not only increased vertebral DEXA and geometry and decreased long bone fractures, but also improved muscle strength, mobility and bone pain (114, 115). Anecdotal use of the drug was widely associated with decreased bone pain, especially in the spine, and increased endurance. However, controlled trials (116-119), while they have

demonstrated the expected increase in vertebral bone density and, more importantly, in vertebral height and area, have not shown an improvement in motor function, strength, or self-reported pain. No controlled trial reported a decreased incidence of long-bone fractures, although two studies obtained downward trends and two reported decreased relative risks when fractures were modeled for initial BMD, gender and OI type using unspecified models. Meta-analyses do not support significant reduction in long bone fractures in children treated with bisphosphonates ([120](#)). In fact, the lack of improvement in fracture rates in the controlled double-blind trial of alendronate led the FDA to specify a labeling change for the drug to indicate that no change in fracture or pain incidence occurred with treatment and that alendronate was not indicated for the treatment of OI ([121](#)). The equivocal improvement in fractures in children is illuminated by data from bisphosphonate treatment of the Brl mouse ([89](#)). Treatment increases bone volume and load to fracture of murine femora, but concomitantly decreases material strength and elastic modulus. Femurs become, ironically, more brittle after prolonged treatment, and bands of mineralized cartilage create matrix discontinuities that decrease bone quality. Prolonged treatment also alters osteoblast morphology. However, pamidronate treatment has not caused osteonecrosis of the jaw in any reported OI cases.

Because of the long half-life of bisphosphonates and the risk of adynamic bone, it is important to use the lowest effective cumulative dose for improved bone density and vertebral geometry. Also, given the balance of bone benefits and detriments, the question arises as to how long children with OI should be treated and what cumulative dose they should receive. Two studies have shown that the maximum effect for bone histology and bone density is achieved in 2-3 years of treatment ([117](#), [122](#)). Also, the interval between cycles is currently the subject of a clinical trial to determine whether a longer cycle interval and thus a lower cumulative dose is equally efficacious. There has also been discussion of when to stop treatment, with some investigators proposing treatment to epiphyseal closure to prevent fractures at the junction of treated and non-treated bone. On the NIH treatment regimen, we have not seen any junctional fractures. Our view is that long-term adynamic bone is a greater detriment than a junctional fracture. We favor a regimen in which children are treated with pamidronate for 3 years, then followed carefully for fractures, bone density and vertebral geometry over the subsequent years. Some children may require another year of treatment at one or two subsequent time point to solidify the gains in bone volume.

The hope that preservation of vertebral geometry in OI children treated with pamidronate would impede the initiation or progress of scoliosis has not been fulfilled. While asymmetric vertebral compressions contribute to scoliosis, improving vertebral height expands thoracic volume but does not

significantly change the incidence or degree of scoliosis in OI types IV and III. This is likely because the laxity of spinal ligaments in OI is still sufficient to lead to scoliosis.

The oral bisphosphonate risedronate has been administered to both children ([123](#)) and adults with OI. A moderate improvement in fractures was reported in children during the first treatment year, but fracture incidence approached that of the placebo group during the 2nd and 3rd years of treatment. Adults treated with risedronate experienced an increase in bone density but not a decrease in fracture incidence ([124](#)).

Bisphosphonates were reported to be marginally effective in type VI OI, caused by PDEF deficiency ([125](#)). It was later postulated ([126](#)) that because bisphosphonates bind to mineralized bone before they are ingested by osteoclasts, the increased amounts of unmineralized osteoid in type VI OI bone might disrupt bisphosphonate deposition. Denosumab, an anti-RANK ligand antibody that inhibits osteoclast activity, was more effective than bisphosphonate in normalizing bone turnover for these patients in a short-term study. Denosumab also has the advantage of a much shorter half-life than pamidronate, 3-4 months vs 10 years. Denosumab treatment studies remain small and uncontrolled. In addition, serious side effects involving altered calcium homeostasis (hypocalcemia on, and rebound hypercalcemia off, treatment) indicate need for further research and development.

Teriparatide, another pharmacologic option to improve bone mineral density, is a human parathyroid hormone analog that has shown preliminary effectiveness in adults with type I OI ([127](#), [128](#)).

Observations of less significant effect in types III and IV OI, possible increased risk for developing osteosarcoma, and more severe bone loss following teriparatide withdrawal have ruled out the use of this drug in the pediatric population and again posit the need for further research ([129](#)).

The use of growth hormone to ameliorate the cardinal feature of short stature in types III and IV OI is still under investigation. Approximately half of the children studied up to 2010 achieved a sustained increase in linear growth of 50% or more over baseline growth rate ([130](#)). Most responders (about 70%) had moderate type IV OI, and higher baseline PICP values. In addition, responders had increased bone formation and density. Patients who respond to growth hormone have increased BMD and improved bone histology (BV/TV). Additional data have supported the positive effect of rGH on BMD and on growth rate, even though rGH studies in patients with OI are rare. Prepubertal patients with mild and moderate OI (types I, IV) were treated for 1 year in a randomized controlled study with the combination of resorption-inhibiting bisphosphonate and anabolic rGH. BMD at the spine and wrist, and overall growth rate were improved, although small sample size precluded conclusions about fracture incidence ([131](#)). Therefore, GH is encouraging as an anabolic therapy. Unfortunately, it will be

applicable to only a subgroup of OI children.

Other drugs that have an anabolic action on bone are in active testing in murine models for OI, since the trials of rGH in pediatric OI were encouraging for effectiveness of anabolic agents. The novel drugs under study are both antibodies, one to sclerostin, a negative regulator of bone formation in the Wnt pathway, and one to TGF-beta, a coordinator of bone remodeling produced by osteoblasts. The neutralizing sclerostin antibody (Scl-Ab) is an anabolic bone drug currently used in clinical osteoporosis trials. Sclerostin is an osteocyte protein that acts on osteoblasts to inhibit bone formation via the canonical wnt signaling pathway. Two weeks of treatment with Scl-Ab increased bone formation rate in the Brl OI murine model, increasing bone mass and improving bone mechanical properties (including fracture risk) without hindering mineralization ([132](#)). Furthermore, five weeks of treatment increased bone formation, bone mass, and bone strength in an adult mouse model of OI ([133](#)). Even after correcting for age, sex, bone mineral content, and body mass index, other studies report lower sclerostin levels in OI-I, III and IV, indicating negative feedback to stop bone loss ([134](#)).

Gene Therapy

Gene therapy of a dominant negative disorder such as OI is not amenable to the replacement approach being employed for recessive enzyme disorders. Dominant negative disorders are disorders of commission; the mutant collagen is synthesized, secreted from the cell and incorporated into matrix, where it actively participates in weakening the structure. Therefore, researchers have used approaches that either suppress expression of mutant collagen or replace mutant cells with donated bone cell progenitors.

The first approach to mutation suppression is modeled on type I OI, in which individuals have a null allele, make half the normal amount of collagen and have mild disease. Specific suppression of expression of the mutant allele, by hammerhead ribozymes, for example, would transform the recipient biochemically from type II, III or IV OI into type I ([135](#)). Although this suppression is complete and specific in vitro, and substantial (50%) and highly selective (90%) in cells, the successful application to animal models is still in development.

The second approach attempts to replicate the natural example of mosaic carriers, who have a substantial proportion of cells heterozygous for the collagen mutation but are clinically normal. They demonstrate that the presence of a substantial burden of mutant cells can be below the threshold of clinical disease. Studies of osteoblasts from mosaic carriers of type III and IV OI have shown that 40-

75% of cells are mutant, setting the threshold for minimal symptoms at 30-40% normal cells ([136](#)). Transplantation studies using murine models have evaluated the potential of mesenchymal stem cells to treat OI. Progenitor cells have been demonstrated to engraft at low levels in oim ([137](#), [138](#)). Most encouraging have been transplantation studies of adult GFP+ bone marrow into Brl mice *in utero*. Despite low engraftment of bone (about 2%), transplantation eliminated the perinatal lethality of Brl mice and improved the biomechanical properties of femora in 2-month old treated Brl mice ([139](#)). However, other murine transplantation studies have indicated a limited regenerative capacity of transplanted cells beyond 6 months ([140](#)). A single human fetus received in utero transplantation of fetal mesenchymal stem-cells; engraftment (0.3%) could still be demonstrated in bone at age 9 months. Evaluation of clinical outcome was complicated by treatment in infancy with bisphosphonate, but the child had sustained fractures and had significant growth deficiency ([141](#)). Bone marrow transplantation of OI children with marrow-derived mesenchymal cells claimed transient improvement in growth, total body mineral content and fractures ([142](#)), but the methodology of these studies was controversial ([143](#)). A final approach is a variant on cell transplantation and involves gene targeting of mutant *COL1A1* and *COL1A2* using adeno-associated vectors in adult mesenchymal stem cells (MSC). This has been successful in less than half of 1% of cells with a *COL1A1* or *COL1A2* mutation, and the production of normal collagen by these targeted cells has been demonstrated. This approach could be potentially valuable for individuals with OI who are past early childhood. However, issues with low targeting success and random integration need to be solved before this approach is suitable for clinical trials ([144](#), [145](#)).

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Late-stage or severe Osteogenesis Imperfecta (OI) involves extreme bone fragility leading to hundreds of fractures, progressive skeletal deformities, severe scoliosis, short stature, and significant mobility impairment. It often presents with severe osteoporosis, hearing loss, and potentially fatal cardiovascular or respiratory complications due to chest wall abnormalities. [[1](#),

Clinical Manifestations of Late-Stage/Severe OI

- **Skeletal Deformities:** Severe, progressive bone deformation (often type III or IV) with extensive bowing of long bones and significant scoliosis.
- **Respiratory Compromise:** Thoracic scoliosis exceeding (60°) degrees, combined with severe rib deformities (pectus carinatum), can lead to fatal respiratory insufficiency or pneumonia.
- **Cardiovascular Issues:** Cardiopulmonary issues, including aortic root dilatation, mitral valve prolapse, and cor pulmonale (right-sided heart failure), are significant causes of mortality in adults.
- **Neurological Complications:** Basilar invagination—the indentation of the skull base by the

spine—can lead to headache, lower cranial nerve palsies, and quadriparesis.

- Mobility Loss: High fracture rates and weak muscles frequently result in complete dependence on wheelchairs. [[1](#), [2](#), [3](#), [4](#)]

Management and Treatment

- Medical Care: Treatment focuses on maximizing mobility and managing complications, including the use of bisphosphonates to improve bone mineral density and reduce bone pain.
- Surgical Intervention: Complex surgeries are often required for spine correction, rod insertion into long bones, and management of basilar invagination.
- Long-term Support: Specialized support for respiratory care and hearing loss is critical. [[1](#), [2](#), [3](#), [4](#), [5](#)]

While severe OI significantly impacts quality of life, management focuses on reducing pain, improving function, and treating complications as they arise.

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