Osteogenesis Imperfecta: Clinical Diagnosis, Nomenclature and Severity Assessment

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Recently, the genetic heterogeneity in osteogenesis imperfecta (OI), proposed in 1979 by Sillence et al., has been confirmed with molecular genetic studies. At present, 17 genetic causes of OI and closely related disorders have been identified and it is expected that more will follow. Unlike most reviews that have been published in the last decade on the genetic causes and biochemical processes leading to OI, this review focuses on the clinical classification of OI and elaborates on the newly proposed OI classification from 2010, which returned to a descriptive and numerical grouping of five OI syndromic groups. The new OI nomenclature and the pre-and postnatal severity assessment introduced in this review, emphasize the importance of phenotyping in order to diagnose, classify, and assess severity of OI. This will provide patients and their families with insight into the probable course of the disorder and it will allow physicians to evaluate the effect of therapy. A careful clinical description in combination with knowledge of the specific molecular genetic cause is the starting point for development and assessment of therapy in patients with heritable disorders including OI.

INTRODUCTION

Osteogenesis imperfecta (OI) is the collective term for a heterogeneous group of connective tissue syndromes characterized primarily by liability to fractures throughout life. Since the first scientific description of OI in 1788 [Peltier, 1981; Baljet, 2002] the nomenclature and classification of OI has evolved substantially.

CLASSIFICATION AND NOMENCLATURE
Osteogenesis Imperfecta 1979: The Original Sillence Classification

The present nosology and classification is based on the publication in 1979 by Sillence et al. [1979] entitled "*Genetic Heterogeneity in*

Osteogenesis Imperfecta". In this epidemiological and genetic study, 180 patients with OI were studied. OI patients were classified in four syndromes by primary clinical characteristics and pattern of inheritance namely (i) Dominantly inherited OI with blue sclerae, (ii) Lethal perinatal OI with radiographically crumpled femora and beaded ribs, (iii) Progressively deforming OI, and (iv) Dominantly inherited OI with normal sclerae. It is of note, that in the manuscript draft no numbers were given to the syndromes, which had been identified. The numbers OI types I–IV[1] were inserted in a table following a meeting with Dr. Victor McKusick who wanted to be able to put these syndromes into the computerized database, Mendelian Inheritance in Man (MIM). As such, the initial types I–IV reflected the order of appearance of the OI groups in the manuscript.

The four OI groups each displayed different modes of inheritance with autosomal dominant the predominant mode of inheritance for group I and IV and at least some families showed autosomal recessive inheritance for OI type II and III, indicating

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[1]In the "Nosology and classification of genetic skeletal disorders" Warrman et al. [2011] recommend using Arabic integers. We agree. However, since this introduction is addressing the historical aspects we have retained the Roman numerals where appropriate for clarity.

genetic heterogeneity in OI. OI type II was subsequently subdivided in OI type II-A, B, and C based on radiological features [Sillence et al., 1984]. In 1983, the first genetic cause of OI, an internal deletion in a collagen gene (*COL1A1*), was described in a patient with OI type II [Chu et al., 1983]. In the following years, mutations in the *COL1A1* and *COL1A2* genes encoding respectively the alpha1 and alpha2 chains of collagen type I were detected in all OI types. As such, the assumption of genetic (locus) heterogeneity in OI was largely abandoned in favor of allelic heterogeneity. It appeared that the specific type and position of the mutation (genotype) did affect the phenotype as had been proposed in the past [Caniggia et al., 1958; Smars, 1961]. However, some OI families remained without an identified genetic defect in the *COL1A1/2* genes [Wallis et al., 1993]. In 2004, an expanded Sillence classification was published by Glorieux and Rauch [Rauch and Glorieux, 2004] adding OI types V–VII with an unknown genetic defect and presumed autosomal dominant inheritance (OI type V) and autosomal recessive inheritance (OI type VI and VII).

In 2006 the first autosomal recessive cause of OI type II was described i.e. *CRTAP* mutations [Barnes et al., 2006]. At present, a total of 17 genetic causes of OI have been described (see Table I, Fig. 1) with *COL1A1/2* mutations still accounting for a large majority of OI patients, approximating 90% in populations of European origin [van Dijk et al., 2012]. Nomenclature revisions have accordingly seen the numbers of OI types being increased up to OI type XIV [Forlino et al., 2011] with the discovery of each new genetic defect. This is confusing in clinical practice since the newly added OI types, result in an OI classification in which the types are not mutually exclusive. OI types I–IV were defined because of specific clinical/radiological characteristics whereas the newer OI types (except for type V) were defined because they involved different gene loci with the clinical/radiological characteristics still being comparable within OI types II–IV [van Dijk et al., 2010].

Osteogenesis Imperfecta 2010: A New OI Nomenclature

At the 2009 meeting of the International Nomenclature group for Constitutional Disorders ICHG of the Skeleton (INCDS) (Published as 2010 Nosology), a decision was finally made to group the known OI syndromes into five groups, that is, preserving the primary four groups and adding OI type V. The importance of the different genetic causes of the OI types was acknowledged by encapsulating the causative genes as subtypes of OI types I–V (Table I) [Warman et al., 2011].

The new nomenclature has also attempted to return to a descriptive grouping of syndromes (Table I) as was the case in the original description of the four OI types, which were defined because of specific clinical characteristics and inheritance pattern. While the ordering is unconventional to those who have used the numerical shorthand for the past 30 years, the order more closely reflects the historical sequence of discovery and has some phenotypic grading reflecting severity. It may be a surprise to some that the former syndrome of OI type IV is designated as Common Variable OI with normal sclerae. This phenotypic variability within families was first noted by Ekman 1788 [Peltier, 1981] and the variability reinforced in the classics of OI in papers by Holcomb [1931] and the doctoral thesis of Seedorf [1949] which reported in detail the variability in families with different syndromes of OI.

The Nosology 2010 grouped OI with the Decreased Bone Density Group of Skeletal Dysplasias [Warman et al., 2011]. In addition to the syndromes with "brittle bones" and/or osteoporosis, encompassed by the descriptive groupings (previously numbered) of osteogenesis imperfecta syndromes, there is the large group of syndromes with decreased bone density, which have significant clinical overlap with the OI syndromes. These syndromes which are characterized by bone fragility and/or osteoporosis alone or with additional features, such as multiple contractures of the large joints as in Bruck syndromes 1 and 2 (Table II) have been included with the OI syndromes since 1992 and will also be included in the 2014 Revised Nosology. Premature aging syndromes in which fractures may be the first manifestation and precede noticeable hair loss, acro-osteolysis and skin aging have been in the main classified with the Acro-osteolyses Group of Disorders.

Because the recommended nosology is phenotypic, yet a numerical classification has been in use for over 30 years we have retained the concept of a short hand but adopted the use of Arabic numerals at this point to replace Roman numerals which were meant to imply distinct gene loci. Furthermore it was apparent from the original paper setting out a numerical nomenclature [Sillence et al., 1979] that the authors both in their discussion and tabulation had concluded that each of these phenotypic groups was likely to be genotypically heterogeneous.

SEVERITY GRADING IN OSTEOGENESIS IMPERFECTA SYNDROMES

In the years following the discovery of *COL1A1/2* mutations in all OI types, the four OI types were often used in clinical practice to reflect severity with mild (OI type 1), lethal (OI type 2), severely deforming (OI type 3), and moderately deforming (OI type 4). Although the INCDS agreed to retain the Sillence classification as "*the prototypic and universally accepted way to classify the degree of severity in OI*" [Warman et al., 2011], the need for internationally agreed criteria for grading severity between affected individuals was proposed and adopted, reflecting also the improved treatment possibilities (surgical, pharmacological and conservative) for patients with OI. The severity grading scale proposed here relies on clinical, historical data, fracture frequency, bone densitometry, and level of mobility (Table III). This severity grading was adopted for the POISE (Pediatric Osteogenesis Imperfecta Safety and Efficacy study) of Risedronate in osteogenesis imperfecta in 231 children ascertained from 22 investigators drawn from 11 countries [Munns and Sillence, 2013; Bishop et al., 2013]. The grading for the POISE study is modified here by the authors with addition of a general guideline to prenatal clinical and ultrasonographic findings. The scale will require further validation by collaboration between Centres of Expertise with sufficient patients and access to facilities for comprehensive assessment in order to further confirm and clarify its clinical utility.

TABLE I. A New OI Nomenclature Combined With Causative Genes (A) Phenotypes With Mild to Moderate Severity, (B) Progressively Deforming and Perinatally Lethal Phenotypes

OI syndrome names	Type	Gene	MIM	Locus	Protein product	Inheritance
[A]						
Non-deforming OI with blue sclerae	1	1. COL1A1	#166200	17q21.33	Collagen alpha-1(I) chain	AD
		2. COL1A2	#166200	7q22.3	Collagen alpha-2(I) chain	AD
Common variable OI with normal sclerae	4	1. COL1A1	#166220	17q21.33	Collagen alpha-1(I) chain	AD
		2. COL1A2	#166220	7q22.3	Collagen alpha-2(I) chain	AD
		3. WNT1[a]	#615220	12q13.12	Wingless-type MMTV integration site family, member 1	AD
					Cartilage-associated protein (CRTAP)	
		1. CRTAP	#610682	3p22.3	Cyclophilin B (CyPB)	AR
		2. PPIB	#259440	15q22.31	Osterix	AR
		3. SP7	#613849	12q13.13	Plastin 3	AR
		1. PLS3		Xq23		XL
OI with calcification in interosseous membranes	5	1. IFITM5	#610967	11p15.5	Interferon-induced transmembrane protein 5	AD
[B]						
Progressively deforming	3	1. COL1A1	#259420	17q21.33	Collagen alpha-1(I) chain	AD
		2. COL1A2	#259420	7q22.3	Collagen alpha-2(I) chain	AD
		1. BMP1	#614856	8p21.3	Bonemorphogeneticprotein 1	AR
		2. CRTAP	#610682	3p22.3	Cartilage-associatedprotein (CRTAP)	AR
		3. FKBP10	#610968	17q21.2	Peptidyl-prolyl cis-transisomerase FKBP10	AR
		4. LEPRE1	#610915	1p34.2	Prolyl 3-hydroxylase 1 (P3H1)	AR
		5. PLOD2	#609220	3q24	Procollagen-lysine, 2-oxoglutarate	AR
		6. PPIB	#259440	15q22.31	5-dioxygenase 2	AR
		7. SERPINF1	#613982	17p13.3	Cyclophilin B (CyPB)	AR
		8. SERPINH1	#613848	11q13.5	Pigment-epithelium-derived factor (PEDF)	AR
		9. TMEM38B	#615066	9q31.1	Heat shock protein 47 (HSP47)	AR
		10.WNT1	#615220	12q13.12	Trimeric intracellular cation channel B (TRIC-B)	AR
		11.CREB3L1		11q11	Wingless-type MMTV integration site family, member 1	AR
					Old Astrocyte	AR
					Specifically induced substance (OASIS)	
Perinatally lethal OI	2[b]	1. COL1A1	#166220	17q21.33	Collagen alpha-1(I) chain	AD
		2. COL1A2	#166220	7q22.3	Collagen alpha-2(I) chain	AD
		1. CRTAP	#610682	3p22.3	Cartilage-associated protein (CRTAP)	AR
		2. LEPRE1	#610915	1p34.2	Prolyl 3-hydroxylase 1 (P3H1)	AR
		3. PPIB	#259440	15q22.31	Cyclophilin B (CyPB)	AR

[a]So far, 12 families with AR OI due to WNT1 mutations have been described. Developmental delay was reported in affected individuals from three families. It is uncertain whether this is part of the clinical phenotype resulting from WNT1 mutations [Fahiminiya et al., 2013; Keupp et al., 2013; Pyott et al., 2013]. A dominant WNT1 mutation appeared to cause early onset osteoporosis [Keupp et al., 2013; Laine et al., 2013].
[b]In clinical practice subdivisions OI type II-A and OI type II-B are still in use. OI type II-A appears to be exclusively caused by heterozygous mutations in the COL1A1/2 genes [van Dijk et al., 2010].
[c]It has been reported that mutations in PLOD2 may also result in progressively deforming OI [Puig-Hervás et al., 2012].

# CLINICAL PRESENTATIONS AND FEATURES OF OSTEOGENESIS IMPERFECTA
Clinical Presentations and Features of OI in General

Primary feature: liability to fractures and osteoporosis. While liability to fractures throughout life is the single most important clinical feature, experience with families with OI type 1 indicate that perhaps 10% of affected individuals have not had a long bone fracture during childhood [Sillence, 1980]. However, newer techniques for measuring bone density, such as dual energy X-ray absorptiometry (DXA) of the skeleton [Lu et al., 1994] and/or more recently peripheral quantative computerized tomography (pQCT) [Gatti et al., 2003; Folkestad et al., 2012] of forearm and leg, frequently reveal significantly reduced bone density in a least one area of the skeleton in those individuals who by formal genetic analysis have OI (Table III).

Net bone fragility is the final result of contributions from primary bone fragility and the secondary fragility resulting from osteoporosis. Osteoporosis develops in the majority of patients with OI. The finding of elevated serum and urine markers of bone
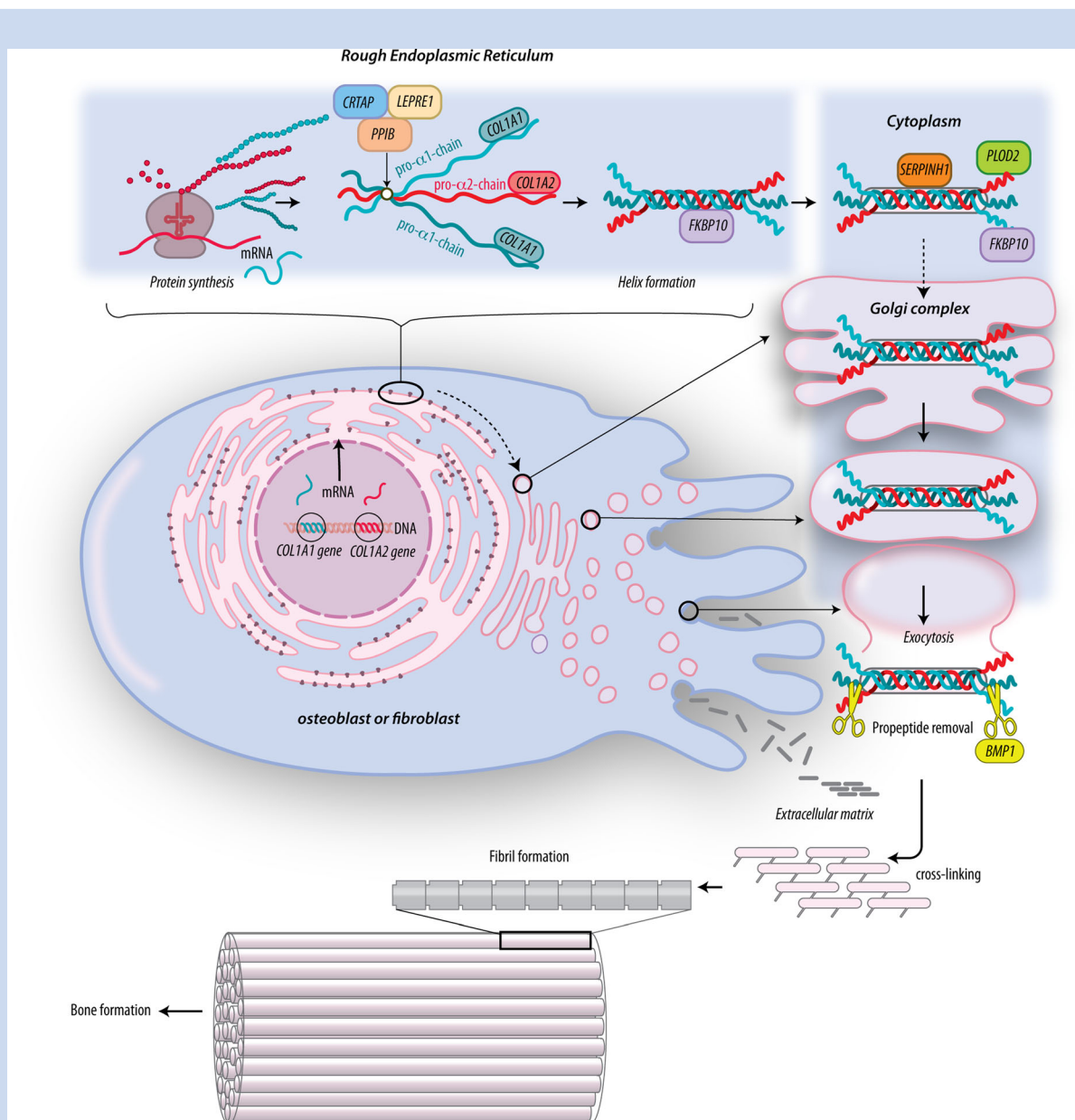
FIG. 1. Overview of collagen type I biosynthesis. Collagen type I consists of two α1-chains and one α2-chain. After translation, pro-α1-chains and pro-α2 chains are processed in the rough Endoplasmic reticulum (rER). These chains have to align in order to start the folding process of (pro)collagen type I into a triple helix. The next step is alignment of the three chains in order to commence folding into a triple helical structure. During this folding process, post-translational modification by specific proteins takes place. The genes encoding proteins involved in post-translational modification and in which mutations have been reported to cause OI, are depicted in this figure. After transport of procollagen type I to the Golgi complex and following exocytosis into the extracellular matrix, cleavage of the C-and N-propeptides results in formation of collagen type I. Subsequently, cross-linking of collagen type I molecules leads to formation of fibrils. Multiple collagen type I fibrils form into collagen fibers, important constituents of bone.

turnover in patients with OI considered along with the findings of bone histomorphometry, is best explained by a combination of increased bone formation and increased bone resorption [Rauch and Glorieux, 2004]. The net effect is a small progressive bone loss since bone resorption is often greater than bone formation, with immobilization also exerting a negative effect on bone formation.

Bisphosphonate treatment aimed at reduction of osteoclast activity, is initiated in many children with OI after careful assessment by the treating physician. In that regard cyclical treatment with intravenous bisphosphonates has become the gold standard for treatment of children with moderate to severe OI. A very recent randomized, double-blind, placebo-controlled trial of oral Risedronate in children with OI, including a large proportion of

TABLE II. Syndromes With Pre-and/or Postnatal Phenotypic Features Overlapping OI

Disorder	MIM	Gene	Locus	Protein Product	Inheritance
Familial doughnut lesions of skull	#126550	Unknown	Unknown	Unknown	AD
Geroderma osteodysplasticum	#231070	GORAB	1q24.2	RAB6-interacting golgin	AR
Gnathodiaphyseal dysplasia (osteopenia with radiolucent lesions of the mandible	#166260	ANO5	11p14.3	Anoctamin-5	AD
Hajdu–Cheney syndrome	#102500	NOTCH2	1p12-p11	Neurogenic locus notch homolog protein 2	AD
Idiopathic juvenile osteoporosis[a]	259750	Unknown	Unknown	Unknown	Unknown
Infantile hypophosphatasia	#241500	ALPL	1p36.12	Alkaline phosphatase, tissue-nonspecific isozyme	AR
OI with congenital joint contractures type 1 (Bruck syndrome type 1)[b]	#259450	FKBP10	17q21.2	Peptidyl-prolyl cis-trans isomerase FKBP10	AR
OI with Congenital Joint Contractures Type 2 (Bruck syndrome type 2)	#609220	PLOD2	3q24	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	AR
Osteogenesis imperfecta with craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features (Cole-carpenter)	112240	Unknown	Unknown	Unknown	AD
Osteoporosis pseudoglioma	#259770	LRP5	11q13.4	Low density lipoprotein-related protein 5	AR
Primary osteoporosis	#259770	LRP5	11q13.4	Low density lipoprotein-related protein 5	AD
Spondylocular syndrome (osteoporosis, cataracts and retinal dysplasia)	605822	Unknown	Unknown	Unknown	AR

[a]Genetically heterogeneous. A small percentage of patients with idiopathic juvenile osteoporosis have been classified as primary genetic osteoporosis with heterozygous mutations in the low density lipoprotein related protein 5 (LRP5). As such, these latter usually have a milder bone disorder than patients with osteoporosis pseudoglioma who have homozygous or compound heterozygous mutations in LRP5 and severe osteoporosis with visual disability [Hartikka et al., 2005].
[b]Recently, recessive mutations in FKBP10 have been described to cause (a) recessive OI most closely resembling OI type III or (b) Bruck syndrome type I [Schwarze et al., 2013].

more mild to moderately affected children, demonstrated a significant reduction in fracture risk, thus extending the therapeutic benefits of this therapy in children with OI [Bishop et al., 2013].

Associated features in general. Associated features in some affected individuals, but not others, include distinct blueness of the sclerae, young adult onset hearing loss, dentinogenesis imperfect (DI), joint hypermobility, short stature, and progressive skeletal deformity. Cardiovascular complications such as valvular dysfunction and aortic root dilatation have been reported in adult OI patients, more often in patients with OI type 3 [Radunovic et al., 2011]. Several associated features are more elaborately described below.

Blue Sclerae. Several major reviews and at least one monograph [Smars, 1961; Sillence et al., 1979; Sillence et al., 1993] concluded that in patients with "blue sclerae" the color of the sclerae is similar to Wedgewood blue in hue and is so very distinctive that the sclerae appear painted. When "blue sclerotics" are present, they remain distinctly blue throughout life.

Berfenstam and Smårs in a population based study [1956] showed that there were statistically significant differences in patterns of phenotypic symptoms and musculoskeletal complications between two groups of patients with OI, those with blue-grey sclerae and those with normal sclerae. Data from a cohort of 95 patients with OI type 1 and OI type 4 in the 1979 Victorian population study were reanalysed to confirm that finding [Sillence et al., 1993].

Attention was also drawn to the misconception that the blue-gray sclerae in OI type 1 are due to the thinning of the sclerae. Eichholtz and Muller [1972] had reported that overall thickness of the sclerae in OI type 1 was normal and there was increased electron dense granular material between scleral collagen fibers. It was proposed that in the pathogenesis of OI type 1, the hearing impairment, easy bruising and possibly the marked joint hypermobility would be best explained by secondary dysregulation of connective tissue composition. There is further evidence that the high prevalence of premature termination/nonsense/splicing mutations which cause the OI type 1 phenotype are associated with alterations in matrix composition [Byers and Cole, 2002].

Dentinogenesis imperfecta. Dentinogenesis imperfecta produces a distinctive yellowing and apparent transparency of the teeth, which are often worn prematurely or broken. Some teeth may have a particularly greyish hue. Radiologic studies of affected teeth show that they have short roots with constricted corono-radicular junctions [Bailleul-Forestier et al., 2008].

Secondary deformations. Skeletal deformities such as scoliosis and basilar impression are regarded as secondary deformations rather than primary malformations. Although the absence of deformity of long bones has been advanced as a diagnostic criterion, the presence of deformity seems at least partly significantly influenced by quality of care. In developing countries, deformity may be evidence of sub-optimal care reflecting lack of primary care services

TABLE III. Pre-and Postnatal Severity Grading Scale of Osteogenesis Imperfecta

Mild OI (Patients with mild OI most often have OI type 1 or 4)
    Ultrasound findings at 20 weeks of pregnancy
        No intra-uterine long bone fractures or bowing
    Postnatal
        Rarely congenital fractures
        Normal or near normal growth velocity and height
        Straight long bones i.e. no intrinsic long bone deformity
        Fully ambulant other than at times of acute fracture
        Minimal vertebral crush fractures
        Lumbar spine bone mineral density Z-score usually >-1.5 (-1.5 to $+1.5$)
        Annualized fracture rate of less than or equal to 1.
        Absence of chronic bone pain or minimal pain controlled by simple analgesics.
        Regular school attendance, i.e., does not miss school due to pain, lethargy, or fatigue.

Moderate OI
    Ultrasound findings at 20 weeks of pregnancy
        Rarely fetal long bone fractures or bowing (but may increase in the last trimester)
    Postnatal (Not modified by bisphosphonate therapy)
        Occasionally congenital fractures
        Decreased growth velocity and height
        Anterior bowing of legs and thighs
        Bowing of long bones related to immobilization for recurrent fractures
        Vertebral crush fractures
        Lumbar spine bone mineral density Z-score usually > -2.5 to <-1.5) but a wide range
        Annualized prepubertal fracture rate greater than 1 (average 3 with a wide range)
        Absent from school due to pain more than 5 days per year.

Severe OI
    Ultrasound findings at 20 weeks of pregnancy
        Shortening of long bones
        Fractures and/or bowing of long bones with some under-modeling
        Slender ribs with absent or discontinuous rib fractures (cases intermediate
    between severe and extremely severe have few rib fractures but crumpled long bones)
        Decreased mineralization
    Postnatal (not modified by bisphosphonate therapy)
        Marked impairment of linear growth
        Wheel-chair dependent
        Progressive deformity of long bones and spine (unrelated to fractures)
        Multiple vertebral crush fractures
        Lumbar spine bone mineral density Z-score usually <-3.0 (wide range with
          age comparison as measurement is size/height dependent)
        Annualized prepubertal fracture rate greater than 3 fractures per annum (age dependent)
        Chronic bone pain unless treated with bisphosphonates
        School attendance characterized by absences for fracture care and fatigue or pain

Extremely Severe OI
    Ultrasound findings at 20 weeks of pregnancy
        Shortening of long bones
        Fractures and/or bowing of long bones with severe under-modeling leading to
    crumpled (concertina-like) long bones
        Thick continuously beaded ribs due to multiple sites of fracture or thin ribs
          (previously described as OI type 2-A and 2-B, respectively)
        Decreased mineralization
    Postnatal
        Thighs held in fixed abduction and external rotation with limitation of movement of most joints
        Clinical indicators of severe chronic pain (pallor, sweatiness, whimpering or grimacing on
          passive movement)
        Decreased ossification of skull, multiple fractures of long bones and ribs. Small thorax.
        Shortened compacted femurs with a concertina-like appearance
        All vertebrae hypoplastic/crushed
        Respiratory distress leading to perinatal death
        Perinatally lethal course

for managing fractures, rather than evidence of an intrinsic process of bone deformation.

Non-Deforming OI With Blue Sclerae—OI Type 1

OI type 1 is characterized by increased bone fragility, which is usually associated with low bone mass, distinctly blue-gray sclerae, and susceptibility to conductive hearing loss commencing in adolescence and young adult life. Deformity of long bones or spine is uncommon and where scoliosis develops it is commonly an idiopathic scoliosis. OI type 1 is the most common variety of OI in European derived communities and has a birth prevalence in the order of 1:25,000 live births and a similar population frequency [Steiner et al., 2013]. Fracture frequency and usually mild long bone and spine deformity mean that it is generally perceived to be of mild severity but occasionally it is moderately severe, particularly when DI is present [Paterson et al., 1983].

DI is observed in some families with this trait and not others. Paterson and colleagues showed that patients with OI type 1 and DI are more likely to have fractures at birth (25% vs. 6%) than those without DI. Furthermore, patients with OI type 1 and DI have a higher fracture frequency, more severe short stature, and more skeletal deformity. Both subgroups have a similar frequency of joint hypermobility, bruising, deafness, and joint dislocations [Paterson et al., 1983].

Hearing impairment resulting from both conductive and sensorineural loss is detectable in over 50% of patients with OI type 1 by 40 years of age [Kuurila et al., 2002; Swinnen et al., 2011]. Vertigo is a troublesome symptom in many people with OI including OI type 1 [Kuurila et al., 2003].

Families with autosomal dominant inheritance and variable expressivity have been reported in many studies. Penetrance for blue sclerae is close to 100% but frequency of clinical fractures is only 90–95% [Smars, 1961; Sillence et al., 1979].

Common Variable OI—OI Type 4

These patients have recurrent fractures, osteoporosis and variable degrees of deformity of long bones and spine but normal sclerae. The sclerae may be bluish at birth but the blue tinge fades during childhood. Hearing impairment is not often encountered. Posterior fossa compression syndromes due to basilar impression with elevation of the floor of the posterior cranial fossa are increased in prevalence. Patients with OI type 4 who have DI have a five times higher relative risk for basilar impression [Sillence, 1994]. Some 30% of patients with OI type 4 have basilar impression on screening but only 16% of these are symptomatic [Sillence, 1994]. Common variable osteogenesis imperfecta with normal sclerae shows occasionally autosomal recessive [van Dijk et al., 2010] and X-linked inheritance [van Dijk et al., 2013] but it is usually inherited as an autosomal dominant disorder (Table I). Severity is highly variable within families. It is not uncommon to find families where there are many affected with mild OI but a few individuals in the same family with moderately severe OI [Holcomb, 1931; Seedorf, 1949].

Progressively Deforming OI–OI Type 3

Individuals with OI type 3 usually have newborn or infant presentation with bone fragility and multiple fractures leading to progressive deformity of the skeleton. They are generally born at or near term and have normal birth weight and often normal birth length, although this may be reduced because of deformities of the lower limbs at birth. Although the sclerae may be blue at birth, observation of many patients with this syndrome documents that the sclerae become progressively less blue with age [Sillence et al., 1986]. Persisting blue sclerae are usually an indication of nonsense or frameshift mutations in type 1 collagen genes characteristic of non-deforming OI type 1 whereas patients with the various autosomal recessive disorders will usually have grey-white sclerae [Byers and Pyott, 2012]. All patients have poor longitudinal growth and fall well below the third centile in height for age and sex. Progressive kyphoscoliosis develops during childhood and progresses into adolescence. Hearing impairment has not been reported in children with this syndrome but hearing loss is more frequent in adults. DI is a variable feature.

At birth, radiographic studies show generalized osteopenia and multiple fractures. Bowing and angulation deformities exist to a variable degree with frequent over-modeling of the shafts of the long bones. Within weeks to months, in some infants, under-modeling of the shafts of long bones results in a "broad-bone" appearance. From several years of age, metaphyses develop increasing density and irregularity. These metaphyseal changes designated a "pop-corn" appearance may evolve only to resolve completely after puberty. The ribs are thin, osteopenic, and progressively crowded as platyspondly increases. The skull shows multiple Wormian bones, although these may not be evident until several weeks to months of age [Sillence et al., 1979; Sillence et al., 1986; Spranger et al., 2003; van Dijk et al., 2011].

In the past, approximately two-thirds of the patients died by the end of the second decade. Death usually resulted from the complications of skeletal chest wall deformity including kyphoscoliosis, pulmonary hypertension, and cardio-respiratory failure. With the present therapeutic options, specifically bisphosphonate treatment with cyclic intravenous Pamidronate [Glorieux et al., 1998] commenced in infancy, it can be expected that today the majority of patients with OI type 3 will survive into adult life. Several studies demonstrate that centers of expertise that manage children with severe OI, achieve very reduced fracture frequency and near normal growth velocity in infants commenced on cyclic intravenous pamidronate by 3 years of age [Plotkin et al., 2000; DiMeglio et al., 2004; Munns et al., 2005; Astrom et al., 2007]. A recent publication confirmed that treatment appears to be well tolerated and associated with an increase in bone density, reduced fracture frequency and improved vertebral shape [Alcausin et al., 2013].

Perinatally Lethal OI Syndromes—OI Type 2

The skeletal, joint, and extraskeletal features of this group of fetuses and children are extremely severe. Perinatal lethality is an outcome rather than a diagnostic feature. Fetuses detected at 18–20 weeks gestation have short crumpled long bones, bowing or angulation deformities of long bones and marked deficiency of ossification of facial and skull bones. At this early gestation, there may be few rib fractures but with each month in utero there is progressive fracturing of ribs resulting in the continuously beaded appearance

combined with crumpled (accordion-like) long bones that is characteristic of the extremely severe end of the spectrum represented by OI type 2 (OI type 2-A) [Sillence et al., 1984]. In our experience, treatment with cyclic intravenous pamidronate is not indicated as bone formation is so impaired and joint restriction so severe there is virtually no chance of any normal childhood life experience. Pain relief with simple analgesics or subcutaneous morphine is particularly valuable, improving comfort and breathing. Among the extraskeletal features in OI type 2, neuropathological findings such as brain migrational defects and/or white matter changes have been reported in a limited number of cases [Emery et al., 1999]. Some babies have a phenotype which is a little less severe with fewer rib fractures (OI type 2-B) [Sillence et al., 1984] and as such they can show overlap with OI type 3 [Spranger, 1984]. Rarely these babies survive, even to adult life and can be "rescued" with treatment with cyclic intravenous pamidronate.

In developed countries, many or most children with OI type 2 are at present diagnosed prenatally (by ultrasound and DNA analysis), often resulting in termination of pregnancy. Mean birth length and weight are less than the fiftieth centile [Sillence et al., 1984]. The thighs are held abducted and in external rotation. The chest is small for gestation and respiratory excursion may be depressed because of the pain from multiple rib fractures and the abnormal biomechanical properties of semicontinuous beading from fracture callus along each rib in the most severely affected. Several clinical features suggest that newborns with OI type 2 are in constant pain. They may have excessive perspiration, pallor, show anxiety at being touched and move their limbs very little because of multiple fractures. One-fifth are stillborn and 90% die by 4 weeks of age [Sillence et al., 1984].

OI With Calcification in Interosseous Membranes—OI Type 5

OI type 5 with moderate to severe bone fragility was originally defined by Battle and Shattock [1908] as a type of OI with progressive calcification of the inter-osseous membranes in the forearms and legs. Independently it was identified by increased propensity to develop hyperplastic callus. The syndrome was delineated in some detail by Bauze et al. [1975], who observed that 10% of patients with moderate to severe OI and normal sclerae, had OI type 5 [Bauze et al., 1975]. In a histomorphometric study of moderately severe OI type 4, 7 of 26 cases (25%) were detected with abnormal bone histomorphometry which is characteristic of OI type 5 [Glorieux et al., 2000]. In clinical studies it accounts for approximately 5% of individuals with OI seen in a hospital setting.

Calcification of the inter-osseous membrane in the forearms is observed from early in life, which leads to restriction of pronation and supination, and eventual dislocation of the radial heads. The sclerae are white and DI and Wormian bones are not present. Those affected tend to have higher serum alkaline phosphatase values and have an increased risk of developing hyperplastic callus following a fracture or orthopaedic surgery. A distinct pathogenesis is further supported by characteristic bone histomorphometry which shows coarse mesh-like lamellation which distinguishes OI type 5 from OI type 4 [Glorieux et al., 2000].

Hyperplastic callus is a rare medical emergency occurring in patients with OI type 5. This is characterized by massive callus with swelling and pain at the site of a fracture, which may be as minor as a stress fracture. Prompt use of indomethacin, an anti-inflammatory COX-1 and COX-2 prostaglandin inhibitor has been recommended to avert progress although of the callus although a randomized clinical trial has not been reported [Glorieux et al., 2000; Cho and Moffat, 2014].

MOLECULAR GENETICS OF OI

Currently, more than 1,000 heterozygous *COL1A1/2* mutations have been identified (https://oi.gene.le.ac.uk, accessed April 1 2013) [Dalgleish, 1997, 1998]. Mutation type and position influence the phenotype and as such genotype–phenotype relations exist to some extent.

Autosomal Dominant OI (OI Types 1-5)

In the majority of affected individuals from European descent, OI types 1–4 result from heterozygous mutations in the *COL1A1/2* genes encoding respectively the alpha1 and alpha2 chains of collagen type I (Fig. 1). The biosynthesis of collagen type I has been depicted in Table III. Sibling recurrence without an affected parent may occur due to gonadal mosaicism for heterozygous dominant mutations in one of the parents [Byers and Cole, 2002].

Patients with OI type 1 and sometimes OI type 4 have an approximately 50% reduction (quantitative or haploinsufficiency effect) in the synthesis of type 1 procollagen often due to heterozygous mutations in one *COL1A1* allele (nonsense, frameshift, and splice site alterations) leading to mRNA instability and haploinsufficiency. Other causes are deletions of the whole *COL1A1* allele or substitutions for glycine by small amino acids (cysteine, alanine, and serine) near the amino-terminal ends of the triple helical domains in either one *COL1A1* or *COL1A2* allele [van Dijk et al., 2012]. Notwithstanding the 50% reduction in collagen synthesis from individual cells, these patients have above average new bone formation, the result of homeostatic mechanisms, which increase the number of bone forming units. This increased new bone formation is linked to increased bone turnover so that the net effect is a small annual bone loss, which is exaggerated if there is immobilization because of fractures or pain [Rauch and Glorieux, 2004].

The majority of cases of OI type 2–4 in North America and Europe are dominantly inherited and most cases are due to heterozygous *COL1A1/2* mutations that result in substitutions for glycine. In general, glycine substitutions near the carboxyl-terminal end appear to result in the severest phenotype. Less common mutations include splice site alterations, insertion/deletion/duplication events that lead to in-frame sequence alterations and variants in the carboxyl-terminal propeptide coding-domains [van Dijk et al., 2012] The heterozygous mutations disrupt triple helical assembly of type I collagen polypeptides, resulting in overprocessing by the enzymes responsible for post-translational modification of (pro) collagen type I and consequently production of abnormal collagen type I. This post-translational over-modification is demonstrable by SDS–polyacrylamide gel electrophoresis. The intertwining of

mutated and normal collagen type I chains result in production of abnormal collagen type I protein, which is rapidly degraded (dominant-negative effect).

Recently, the genetic cause of OI type 5 has been elucidated in two independent publications [Cho et al., 2012; Semler et al., 2012] and consists of a heterozygous C>T transition in the 5′UTR (untranslated region) of *IFITM5* (c.-14C>T). *IFITM5* encodes Interferon induced transmembrane protein 5, the expression of this protein has been shown to peak during osteoblast formation in the early mineralization stage in mice and rats [Hanagata et al., 2011].

Autosomal Recessive OI (OI types 2-4)

A severe, autosomal recessive form of OI type 3 with a comparatively high frequency had already been recognized in the past in the black populations of southern Africa [Wallis et al., 1993] (Table III). Nowadays, it is also known that a founder mutation in *LEPRE1* is carried by 1.5% of West Africans and 0.4% of African Americans [Cabral et al., 2012]. Recessive mutations in genes involved in collagen type I biosynthesis and post-translational modification have been identified in OI types 2–4 in the last 6 years. These were recently reviewed in depth [Byers and Pyott, 2012]. The recessive mutations concern genes encoding proteins involved in collagen type I biosynthesis, can be subdivided into (i) an enzymatic complex responsible for 3-prolyl hydroxylation of one specific residue (P986) in the alpha1 chain [van Dijk et al., 2012] and probably for initiating chain alignment and helical folding [Pyott et al., 2011] (*CRTAP*, *LEPRE1*, *PPIB*); (ii) quality control check of the collagen triple helix (*SERPINH1*, *FKBP10*); (iii) late processing of folded (pro) collagen type I chains i.e. hydroxylation of lysine residues in triple helical telopeptides important for collagen type I cross-linking in bone [van Dijk et al., 2012] (*PLOD2*, *FKBP10*) and cleavage of the C-propeptide *(BMP1)* [Martínez-Glez et al., 2012] (Fig. 1).

Furthermore, recessive mutations have been reported in *SP7* encoding Osterix, an osteoblast specific transcription factor, in *SERPINF1* possibly involved in bone formation and remodeling [van Dijk et al., 2012] and in *TMEM38B* encoding a trimeric intracellular cation channel [Shaheen et al., 2012; Volodarsky et al., 2013].

The recent delineation of mutations in *WNT1*, encoding a signaling peptide involved in osteoblast differentiation and proliferation [Fahiminiya et al., 2013; Keupp et al., 2013; Laine et al., 2013] and the interaction with FRIZZLED and its coligand LRP5, in which mutations in the latter are known to result in patients with severe syndromic OI, predict that further study of patients with severe OI from endogamous populations will uncover mutational mechanisms in the subsequent steps of the WNT-Beta Catenin signaling pathway. Most recently, a homozygous deletion of *CREB3L1* was identified in a family with a severe progressively deforming OI phenotype. *CREB3L1* encodes the ER-stress transducer OASIS that has been shown in a murine model to bind to the osteoblast-specific UPRE (unfolded protein response element) regulatory region in the *Col1a1* promotor. This finding expands the genetic heterogeneity in OI and illustrates the role of ER-stress in the pathophysiology of OI [Symoens et al., 2013].

Pathogenic mutations found in recessive genes (Dalgleish, R: Osteogenesis Imperfecta Variant Database (https://oi.gene.le.ac.uk,

accessed April 1 2013), are mostly homozygous or compound heterozygous loss-of-function mutations that result in two null alleles with severely decreased or no production of normal protein.

X-linked OI

X-linked inheritance of osteoporosis and fractures had been reported only once in the thesis of D. Sillence (Pedigree 41, Appendix) [Sillence, 1980]. Recently, loss-of-function mutations in *PLS3* encoding plastin-3 were discovered as a cause of one form of X-linked osteoporosis with fractures [van Dijk et al., 2013]. In hemizygous men, pathogenic mutations in *PLS3* were associated with osteoporosis and osteoporotic fractures of the axial and appendicular skeleton usually developing in childhood. The clinical picture in heterozygous female members was variable and ranged from normal bone mineral density and an absence of fractures to early-onset osteoporosis. No extraskeletal features of OI were present in affected men, but the phenotype is indistinguishable in many patients with other types of OI, it would probably fit best in the common variable OI (OI type 4) group, of whom less than 50% of patients have features such as Wormian bones in the skull and the sclerae are normal in hue, bluish in childhood and fading to normal adult hue.

CONCLUSION

From a medical geneticist point of view, the core principle is phenotyping of individuals (dysmorphology) and the study of these families with regard to inheritance pattern and phenotypic variability. The OI classification from 1979 is a classic example of the importance and possibilities of dysmorphology since it led to the delineation of four OI syndromes based on clinical/radiological features and inheritance, in combination with the assumption that OI was genetically heterogeneous, which was confirmed many years later by molecular genetic studies.

At present time, it has been postulated that molecular techniques such as Next-Generation Sequencing will decrease the need for phenotyping. However, the new OI nomenclature and the Severity Grading Scale described in this paper, emphasize the importance of phenotyping in order to diagnose, classify and assess severity of OI. This will provide patients and their families with insight into the probable course of the disorder and it will allow physicians to evaluate the effect of therapy. A careful clinical description in combination with knowledge of the specific molecular genetic cause is the starting point for development and assessment of therapy in patients with heritable disorders including OI. The latter is the biggest challenge we face in the upcoming decade(s).

When it comes to development of pharmacological therapy for OI, Professors DeVogaeler, Eva Astrom, and Francis Glorieux and colleagues have been of great importance in advancing a therapeutic praxis. In the fields of collagen biochemistry and molecular biology, Peter Byers, MD and his collaborator Dr. Ulrike Schwarze and their many colleagues at Centre for Collagen Research Seattle Washington, Hans-Peter Bachinger, PhD and colleagues, Shriners Portland Oregon, Joan Marini, MD, PhD and colleagues, Bethesda, Maryland, Dr. Raymond Dalgleish in Leicester, United Kingdom and Gerard Pals, PhD in Amsterdam, the Netherlands, have made outstanding contributions in taking the field of osteogenesis imperfecta forward. Of course many others, not specifically named must be acknowledged for their contribution to the field of OI.

REFERENCES

Alcausin MB, Ault J, Briody J, Pacey V, Mcquade M, Bridge C, Engelbert RHH, Sillence DO, Munns CF. 2013. Intravenous pamidronate treatment in children with moderate-to-severe osteogenesis imperfecta started under three years of age. Horm Res Paediatr 79:333–340.

Astrom E, Jorulf H, Soderhall S. 2007. Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. Arch Dis Child 92:332–338.

Bailleul-Forestier I, Berdal A, Vinchier F, de Ravel T, Fryns JP, Verloes A. 2008. The genetic basis of inherited anomalies of the teeth. Part 2: syndromes with significant dental development. EJMG 51:383–408.

Baljet B. 2002. Aspects of the history of osteogenesis imperfecta (Vrolik's syndrome). Ann Anat 184:1–7.

Barnes AM, Chang W, Morello R, Cabral WA, Weis M, Eyre DR, Leikin S, Makareeva E, Kuznetsova N, Uveges TE, Ashok A, Flor AW, Mulvihill JJ, Wilson PL, Sundaram UT, Lee B, Marini JC. 2006. Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. N Engl J Med 355:2757–2764.

Battle WH, Shattock SG. 1908. A remarkable case of diffuse cancellous osteoma of the femur, following a fracture, in which similar growths afterwards developed in connection with other bones. Proc R Soc Med 1:83–115.

Bauze RV, Smith R, Francis MJO. 1975. A new look at osteogenesis imperfecta. A clinical, radiological and biochemical study of forty-two patients. J Bone Joint Surg 57B:2.

Berfenstam R, Smars G. 1956. Osteogenesis imperfecta: A survey with some results from an introductory study of the incidence of the disease in Sweden. Sven Lakartidn 53:2113–2123.

Bishop N, Adami S, Ahmed SF, Antón J, Arundel P, Burren CP, Devogelaer J, Hangartner T, Hosszú E, Lane JM, Lorenc R, Mäkitie O, Munns CF, Paredes A, Pavlov H, Plotkin H, Raggio CL, Reyes ML, Schoenau E, Semler O, Sillence DO, Steiner RD. 2013. Risedronate in children with osteogenesis imperfecta: A randomised, double-blind, placebo-controlled trial. Lancet 382:1424–1432.

Byers P, Cole W. 2002. Osteogenesis imperfecta. In: Royce PM, Steinmann B, editors. Connective tissue and its heritable disorders. New York, NY: Wiley-Liss. pp. 385–430.

Byers PH, Pyott SM. 2012. Recessively inherited forms of osteogenesis imperfecta. Annu Rev Genet 46:475–497.

Cabral WA, Barnes AM, Adeyemo A, Cushing K, Chitayat D, Porter FD, Panny SR, Gulamali-Majid F, Tishkoff SA, Rebbeck TR, Gueye SM, Bailey-Wilson JE, Brody LC, Rotimi CN, Marini JC. 2012. A founder mutation in LEPRE1 carried by 1.5% of West Africans and 0.4% of African Americans causes lethal recessive osteogenesis imperfecta. Genet Med 14:543–551.

Caniggia A, Stuart C, Guideri R. 1958. Fragilitas ossium hereditaria tarda: Ekman-Lobstein disease. Acta Med Scand Suppl 340:1–172.

Cho TJ, Lee KE, Lee SK, Song SJ, Kim KJ, Jeon D, Lee G, Kim HN, Lee HR, Eom HH, Lee ZH, Kim OH, Park WY, Park SS, Ikegawa S, Yoo WJ, Choi IH, Kim JW. 2012. A single recurrent mutation in the 5′-UTR of IFITM5 causes osteogenesis imperfecta type V. Am J Hum Genet 91:343–348.

Cho TJ, Moffat P. 2014. Osteogenesis imperfecta type V. In: Shapiro J, Byers P, Glorieux F, Sponseller P, editors. Osteogenesis imperfecta: A translational approach to brittle bone disease. 1st edition. London, UK: Academic Press.

Chu ML, Williams CJ, Pepe G, Hirsch JL, Prockop DJ, Ramirez F. 1983. Internal deletion in a collagen gene in a perinatal lethal form of osteogenesis imperfecta. Nature 304:78–80.

Dalgleish R. 1997. The human type I collagen mutation database. Nucleic Acids Res 25:181–187.

Dalgleish R. 1998. The human collagen mutation database 1998. Nucleic Acids Res 26:253–255.

DiMeglio LA, Ford L, McClintock C, Peacock M. 2004. Intravenous pamidronate treatment of children under 36 months of age with osteogenesis imperfecta. Bone 35:1038–1045.

Eichholtz W, Muller D. 1972. Electron microscopy findings on the cornea and sclera in osteogenesis imperfecta. Klin Monbl Augenheilkd 161:646–653.

Emery SC, Karpinski NC, Hansen L, Masliah E. 1999. Abnormalities in central nervous system development in osteogenesis imperfecta type II. Pediatr Dev Pathol 2:124–130.

Fahiminiya S, Majewski J, Mort M, Mofatt P, Glorieux FH, Rauch F. 2013. Mutations in WNT1 are a cause of osteogenesis imperfecta. J Med Genet 50:345–348.

Folkestad L, Hald JD, Hansen S, Gram J, Langdahl B, Abrahamsen B, Brixen K. 2012. Bone geometry, density, and microarchitecture in the distal radius and tibia in adults with osteogenesis imperfecta type I assessed by high-resolution pQCT. J Bone Miner Res 27:1405–1412.

Forlino A, Cabral WA, Barnes AM, Marini JC. 2011. New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol 7:540–557.

Gatti D, Colapietro F, Fracassi E, Sartori E, Antoniazzi F, Braga V, Rossini M, Adami S. 2003. The volumetric bone density and cortical thickness in adult patients affected by osteogenesis imperfecta. J Clin Densitom 6:173–177.

Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. 1998. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med 339:947–952.

Glorieux FH, Rauch F, Plotkin H, Ward L, Travers R, Roughley P, Lalic L, Glorieux DF, Fassier F, Bishop NJ. 2000. Type V osteogenesis imperfecta: A new form of brittle bone disease. J Bone Miner Res 15:1650–1658.

Hanagata N, Li X, Morita H, Takemura T, Li J, Minowa T. 2011. Characterization of the osteoblast-specific transmembrane protein IFITM5 and analysis of IFITM5-deficient mice. J Bone Miner Metab 29:279–290.

Hartikka H, Mäkitie O, Männikkö M, Doria AS, Daneman A, Cole WG, Ala-Kokko L, Sochett EB. 2005. Heterozygous mutations in the LDL receptor-related protein 5 (LRP5) gene are associated with primary osteoporosis in children. J Bone Miner Res 20:783–789.

Holcomb DY. 1931. A fragile boned family. J Hered 22:105.

Keupp K, Beleggia F, Kayserili H, Barnes AM, Steiner M, Semler O, Fischer B, Yigit G, Janda CY, Becker J, Breer S, Altunoglu U, Grünhagen J, Krawitz P, Hecht J, Schinke T, Makareeva E, Lausch E, Cankaya T,

Caparrós-Martín JA, Lapunzina P, Temtamy S, Aglan M, Zabel B, Eysel P, Koerber F, Leikin S, Garcia KC, Netzer C, Schönau E, Ruiz-Perez VL, Mundlos S, Amling M, Kornak U, Marini J, Wollnik B. 2013. Mutations in WNT1 cause different forms of bone fragility. Am J Hum Genet 92:565–574.

Kuurila K, Kaitila I, Johansson R, Grenman R. 2002. Hearing loss in Finnish adults with osteogenesis imperfecta: A nationwide survey. Ann Otol Rhinol Laryngol 111:939–946.

Kuurila K, Kentala E, Karjalainen S, Pynnönen S, Kovero O, Kaitila I, Grénman R, Waltimo J. 2003. Vestibular dysfunction in adult patients with osteogenesis imperfecta. Am J Med Genet Part A 120A:350–358.

Laine CM, Joeng KS, Campeau PS, Kiuranta R, Tarkkonen K, Grover M, Lu JT, Pekkinen M, Wessman M, Heino TJ, Nierminen-Pihala V, Aronen M, Laine T, Kröger H, Cole WG, Lehesjoki A, Nevarez L, Krakow D, Curry CJR, Cohn DH, Gibbs RA, Lee BH, Mäkitie O. 2013. WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta. N Engl J Med 368:1809–1847.

Lu PW, Briody JN, Ogle GD, Morley K, Humphries IR, Allen J, Howman-Giles R, Sillence D, Cowell CT. 1994. Bone mineral density of total body, spine, and femoral neck in children and young adults: A cross-sectional and longitudinal study. J Bone Miner Res 9:1451–1458.

Martínez-Glez V, Valencia M, Caparrós-Martín JA, Aglan M, Temtamy S, Tenorio J, Pulido V, Lindert U, Rohrbach M, Eyre D, Giunta C, Lapunzina P, Ruiz-Perez VL. 2012. Identification of a mutation causing deficient BMP1/mTLD proteolytic activity in autosomal recessive osteogenesis imperfecta. Hum Mutat 33:343–350.

Munns CF, Rauch F, Travers R, Glorieux FH. 2005. Effects of intravenous pamidronate treatment in infants with osteogenesis imperfecta: Clinical and histomorphometric outcome. J Bone Miner Res 20:1235–1243.

Munns CR, Sillence D. 2013. Osteogenesis imperfecta (and other disorders of bone matrix). In: Rimoin DL, Pyeritz PE, Korf BR, editors. Emery and Rimoin's principles and practice of medical genetics. Oxford, UK: Academic Press.

Paterson CR, McAllion S, Miller R. 1983. Heterogeneity of osteogenesis imperfecta type I. J Med Genet 20:203–205.

Peltier LF. 1981. The classic: Congenital osteomalacia. Olaus Jacob Ekman. Clin Orthop Relat Res 3–5.

Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, Glorieux FH. 2000. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. J Clin Endocrinol Metab 85:1846–1850.

Puig-Hervás MT, Temtamy S, Aglan M, Valencia M, Martínez-Glez V, Ballesta-Martínez MJ, López-González V, Ashour AM, Amr K, Pulido V, Guillén-Navarro E, Lapunzina P, Caparrós-Martín JA, Ruiz-Perez VL. 2012. Mutations in PLOD2 cause autosomal-recessive connective tissue disorders within the Bruck syndrome—osteogenesis imperfecta phenotypic spectrum. Hum Mutat 33:1444–1449.

Pyott SM, Schwarze U, Christiansen HE, Pepin MG, Leistritz DF, Dineen R, Harris C, Burton BK, Angle B, Kim K, Sussman MD, Weis M, Eyre DR, Russell DW, McCarthy KJ, Steiner RD, Byers PH. 2011. Mutations in PPIB (cyclophilin B) delay type I procollagen chain association and result in perinatal lethal to moderate osteogenesis imperfecta phenotypes. Hum Mol Genet 20:1595–1609.

Pyott SM, Tran TT, Leistritz DF, Pepin MG, Mendelsohn NJ, Temme RT, Fernandez BA, Elsayed SM, Elsobky E, Verma I, Nair S, Turner EH, Smith JD, Jarvik GP, Byers PH. 2013. WNT1 mutations in families affected by moderately severe and progressive recessive osteogenesis imperfecta. Am J Hum Genet 92:590–597.

Radunovic Z, Wekre LL, Diep LM, Steine K. 2011. Cardiovascular abnormalities in adults with osteogenesis imperfecta. Am Heart J 161:523–529.

Rauch F, Glorieux FH. 2004. Osteogenesis imperfecta. Lancet 363:1377–1385.

Schwarze U, Cundy T, Pyott SM, Christiansen HE, Hegde MR, Bank RA, Pals G, Ankala A, Conneely K, Seaver L, Yandow SM, Raney E, Babovic-Vuksanovic D, Stoler J, Ben-Neriah Z, Segel R, Lieberman S, Siderius L, Al-Aqeel A, Hannibal M, Hudgins L, McPherson E, Clemens M, Sussman MD, Steiner RD, Mahan J, Smith R, Anyane-Yeboa K, Wynn J, Chong K, Uster T, Aftimos S, Sutton VR, Davis EC, Kim LS, Weis MA, Eyre D, Byers PH. 2013. Mutations in FKBP10, which result in Bruck syndrome and recessive forms of osteogenesis imperfecta, inhibit the hydroxylation of telopeptide lysines in bone collagen. Hum Mol Genet 22:1–17.

Seedorf KS. 1949. Osteogenesis imperfecta. A study of clinical features and heredity based on 55 Danish families comprising 18 affected members. Copenhagen, Denmark: Universitetsforlaget Aarhus.

Semler O, Garbes L, Keupp K, Swan D, Zimmermann K, Becker J, Iden S, Wirth B, Eysel P, Koerber F, Schoenau E, Bohlander SK, Wollnik B, Netzer C. 2012. A mutation in the 5′-UTR of IFITM5 creates an in-frame start codon and causes autosomal-dominant osteogenesis imperfecta type V with hyperplastic callus. Am J Hum Genet 91:349–357.

Shaheen R, Alazami AM, Alshammari MJ, Faqeih E, Alhashmi N, Mousa N, Alsinani A, Ansari S, Alzahrani F, Al-Owain M, Alzayed ZS, Alkuraya FS. 2012. Study of autosomal recessive osteogenesis imperfecta in Arabia reveals a novel locus defined by TMEM38B mutation. J Med Genet 49:630–635.

Sillence DO. 1980. Bone dysplasia. Genetic and ultrastructural aspects with reference to osteogenesis imperfecta. Ann Arbor, Michigan: University Microfilms.

Sillence DO. 1994. Craniocervical abnormalities in osteogenesis imperfecta: Genetic and molecular correlation. Pediatr Radiol 24:427–430.

Sillence DO, Senn A, Danks DM. 1979. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

Sillence DO, Barlow KK, Garber AP, Hall JG, Rimoin DL. 1984. Osteogenesis imperfecta type II delineation of the phenotype with reference to genetic heterogeneity. Am J Med Genet 17:407–423.

Sillence DO, Barlow KK, Cole WG, Dietrich S, Garber AP, Rimoin DL. 1986. Osteogenesis imperfecta type III. Delineation of the phenotype with reference to genetic heterogeneity. Am J Med Genet 23:821–832.

Sillence DO, Butler B, Latham M, Barlow K. 1993. Natural history of blue sclerae in osteogenesis imperfecta. Am J Med Genet 45:183–186.

Smars G. 1961. Osteogenesis imperfecta in Sweden. Clinical, genetic, epidemiological and socio-medical aspects. Stockholm, Sweden: Scandinavian University Books.

Spranger J. 1984. Invited editorial comment: Osteogenesis imperfecta: A pasture for splitters and lumpers. Am J Med Genet 17:425–428.

Spranger J, Brill P, Poznanski A. 2003. Bone dysplasias. An atlas of genetic disorders of skeletal development. Oxford, UK: Oxford University Press.

Steiner RD, Adsit J, Basel D. 2013. COL1A1/2-Related Osteogenesis Imperfecta. Genereviews [w w w.ncbi.nlm.nih.gov/books/NBK1295/].

Swinnen FK, Coucke PJ, De Paepe AM, Symoens S, Malfait F, Gentile FV, Sangiorgi L, D'Eufemia P, Celli M, Garretsen TJ, Cremers CW, Dhooge IJ, De Leenheer EM. 2011. Osteogenesis imperfecta: The audiological phenotype lacks correlation with the genotype. Orphanet J Rare Dis 6:88.

Symoens S, Malfait F, D Hondt S, Callewaert B, Dheedene A, Steyaert W, Bächinger HP, De Paepe A, Kayserili H, Coucke PJ. 2013. Deficiency for the ER-stress transducer OASIS causes severe recessive osteogenesis imperfecta in humans. Orphanet J Rare Dis 8:154.

van Dijk FS, Byers PH, Dalgleish R, Malfait F, Maugeri A, Rohrbach M, Symoens S, Sistermans EA, Pals G. 2012. EMQN Best practice guidelines

for the laboratory diagnosis of osteogenesis imperfecta. Eur J Hum Genet 20:11–19.

van Dijk FS, Cobben JM, Kariminejad A, Maugeri A, Nikkels PG, van Rijn RR, Pals G. 2011. Osteogenesis imperfecta: A review with clinical examples. Mol Syndromol 2:1–20.

van Dijk FS, Pals G, van Rijn RR, Nikkels PG, Cobben JM. 2010. Classification of osteogenesis imperfecta revisited. Eur J Med Genet 53:1–5.

van Dijk FS, Zillikens MC, Micha D, Riessland M, Marcelis CLM, de Die-Smulders CE, Milbradt J, Franken AA, Harsevoort AJ, Lichtenbelt KD, Pruijs HE, Rubio-Gozalbo ME, Zwertbroek R, Moutaouakil Y, Egthuijsen J, Hammerschmidt M, Bijman R, Semeins CM, Bakker AD, Everts V, Klein-Nulend J, Campos-Obando N, Hofman A, te Meerman GF, Verkerk AJMH, Uitterlinden AG, Maugeri A, Sistermans EA, Waisfisz Q, Meijers-Heijboer H, Wirth B, Simon MEH, Pals G.

2013. PLS3 mutations in X-linked osteoporosis and fractures. Accepted for publication in N Eng J Med 369:1529–1536.

Volodarsky M, Markus B, Cohen I, Staretz-Chacham O, Flusser H, Landau D, Shelef I, Langer Y, Birk OS. 2013. A deletion mutation in TMEM38B associated with autosomal recessive osteogenesis imperfecta. Hum Mutat 34:582–586.

Wallis GA, Sykes B, Byers PH, Mathew CG, Viljoen D, Beighton P. 1993. Osteogenesis imperfecta type III: Mutations in the type I collagen structural genes, COL1A1 and COL1A2, are not necessarily responsible. J Med Genet 30:492–496.

Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, Mortier G, Mundlos S, Nishimura G, Rimoin DL, Robertson S, Savarirayan R, Sillence D, Spranger J, Unger S, Zabel B, Superti-Furga A. 2011. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet Part A 155A:943–968.