Bone 126 (2019) 11–17

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

# Mendelian bone fragility disorders☆

Marie-Eve Robinson, Frank Rauch*

*Shriners Hospital for Children, Montreal, Quebec, Canada*

ARTICLE INFO

*Keywords:*
Collagen type I
Fractures
Osteoblast
Osteogenesis imperfecta
Sequencing

ABSTRACT

Mendelian bone fragility disorders are caused by genetic variants that can be inherited in an autosomal dominant, autosomal recessive or X-linked manner and have a large detrimental effect on bone strength. As a rule, the more damaging the genetic defect is, the earlier the first fracture will occur, typically during bone development. This review focusses on conditions where bone fragility is the most conspicuous characteristic, of which osteogenesis imperfecta (OI) is the best-known disorder. The large majority of individuals with an OI phenotype have disease-causing dominant variants in *COL1A1* or *COL1A2*, the genes coding for collagen type I. Interestingly, large sequencing databases indicate that there are about 10 times more carriers of *COL1A1/COL1A2* variants that should lead to OI than there are individuals with a diagnosis of OI. It is possible that at least some of these variants lead to incomplete OI phenotypes and are diagnosed as osteoporosis during adulthood. Apart from mutations affecting collagen type I production, biallelic mutations in *LRP5* and *WNT1* can cause very rare and severe bone fragility disorders. Heterozygous pathogenic variants in these genes are much more common and can cause the clinical picture of primary osteoporosis. As sequencing studies are more widely performed in adults with bone fragility disorders, evidence is emerging that what appears as primary osteoporosis in fact can be due to mutations in bona fide OI genes. The distinction between OI and primary osteoporosis is therefore likely to blur in future.

## 1. Introduction

Fractures are common during skeletal development. According to a study from the United Kingdom 30% of boys and 19% of girls will have a fracture before the age of 18 years [1]. About 60% of these fractures occur at three upper extremity sites (radius/ulna, carpal bones, humerus). Fracture incidence peaks at around the time of the pubertal growth spurt and rapidly declines thereafter. By the age of 17 years, fracture rates are 65% below their pubertal peak in girls and 35% below their pubertal maximum in boys [1].

Even though the high fracture rate during growth is likely to be multifactorial, variations in the ability of bone to withstand mechanical forces (bone strength) may play a role. In growing long bones, cortices at the metaphysis are thin and cortical porosity is elevated compared to adults [2,3]. As these structural 'deficits' during skeletal growth are likely to cause relative bone weakness, they may contribute to the high fracture rates in children.

Mendelian bone fragility disorders are caused by genetic variants that can be inherited in an autosomal dominant, autosomal recessive or X-linked manner [4]. These variants have a large detrimental effect on bone strength and thus can lead to fractures in the presence of minimal trauma or even without obvious trauma. The effect of genetic variants associated with monogenic bone fragility disorders is often orders of magnitude larger than the effect of variants that have been identified by genome-wide association studies (GWAS). For example, children and adolescents with osteogenesis imperfecta (OI), the prototypical monogenic bone fragility disorder, have 11 times (1100%) more fractures than the general population of the same age and sex [5]. In comparison, the genetic risk factors for fractures that have been identified by GWAS increase fracture risk by 10% or less [6]. The overall number of fractures understates the disease burden associated with OI, as the fracture distribution is skewed towards more severe fractures. For example, the rate of femur fractures in children and adolescents even with mild OI is increased by about 90 fold [5,7].

The phenotypic range of Mendelian bone fragility disorders is very wide. As a rule, the earlier the first fracture occurs, the more detrimental the effect of the genetic variant on bone strength. In the most severe bone fragility disorders fractures occur in utero [8]. Individuals with mild forms of heritable bone fragility may sustain fractures only in adult life or not at all. Nevertheless, monogenic bone fragility disorders often become manifest during childhood, and most of the information about these conditions stems from pediatric studies. The present review

☆ This study was supported by the Shriners of North America Fonds de Recherche du Québec - Santé
* Corresponding author at: Shriners Hospital for Children, 1003 Decarie, Montreal, Quebec H4A 0A9, Canada.
*E-mail address:* frauch@shriners.mcgill.ca (F. Rauch).

https://doi.org/10.1016/j.bone.2019.04.021
Received 7 April 2019; Accepted 26 April 2019
Available online 27 April 2019

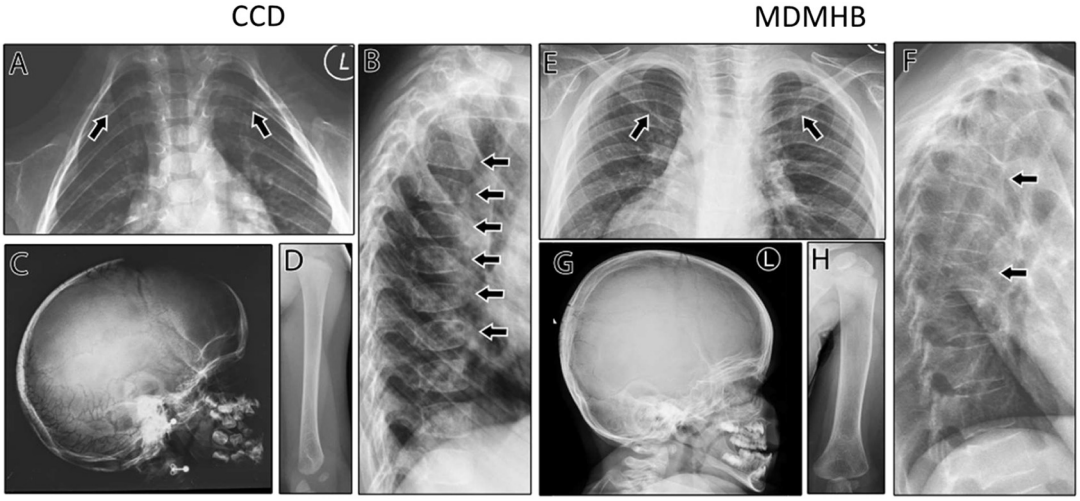


**Fig. 1.** Skeletal characteristics of two bone dysplasias related to *RUNX2* mutations, cleidocranial dysplasia (CCD) and metaphyseal dysplasia with maxillary hypoplasia and brachydactyly (MDMHB). (A -D) CCD caused by a heterozygous loss of function mutation in *RUNX2* (frameshift), leading to clavicular hypoplasia (A), vertebral deformities (B), Wormian bones and crowded teeth (C), but a normally shaped humerus (D). (E to H) MDMHB caused by heterozygous gain of function in *RUNX2* (intragenic duplication of exon 3 to 5), leading to enlarged medial portions of the clavicles (E), vertebral deformities (F), thick cranial vault and maxillary hypoplasia (G), and undermodeled diaphysis and metaphysis of the humerus (H). Despite contrasting phenotypic features, both conditions are associated with bone fragility.

therefore largely focusses on genetic defects leading to fractures during childhood but will also discuss some implications for genetic studies on bone fragility disorders in adults.

## 2. Classification of Mendelian bone fragility disorders

Mendelian disorders associated with fractures can be classified into conditions where bone fragility is the most conspicuous characteristic, and diseases where bone fragility is part of a broader phenotype. Among the latter, fractures can be a feature of bone dysplasias that have primary abnormalities in bone shape and low bone mass, such as Hajdu-Cheney syndrome (caused by heterozygous mutations in exon 34 of *NOTCH2*), cleidocranial dysplasia (heterozygous *RUNX2* loss of function mutations) or metaphyseal dysplasia with maxillary hypoplasia and brachydactyly (heterozygous *RUNX2* intragenic duplications) [9–11] (Fig. 1). Fractures also occur frequently in several types of osteopetrosis, a Mendelian disorder with excessively high bone mass, highlighting the importance of factors other than bone mass in the pathogenesis of heritable bone fragility [12]. Monogenic disorders that mainly affect other organs but also lead to elevated fracture rates include neuromuscular disorders such as Duchenne muscular dystrophy and spinal muscular atrophy [13,14], as well as inborn errors of metabolism such as Gaucher disease [15]. Overall, most long-lasting conditions in children affect some aspect of bone development and therefore many chronic pediatric disorders lead to bone fragility as a secondary characteristic [16].

This review focusses on conditions where bone fragility is the most conspicuous characteristic. The diagnostic categories used for such disorders are usually OI and 'conditions similar to OI', for which terms such as juvenile osteoporosis or early-onset osteoporosis are commonly used. The terminology for the conditions in this field is somewhat inconsistent, mostly reflecting whether authors focus on the clinical phenotype, as proposed by the Skeletal Dysplasia Nomenclature Group [17] or on the disease-causing gene, as favored in the Online Mendelian Inheritance in Man database (https://omim.org). A list of bone fragility genes and the related diagnoses is given in Table 1.

Mutations directly affecting the collagen type I encoding genes, *COL1A1* and *COL1A2*, are by far the most common monogenic causes of fractures in children [18,19]. As many other factors are involved in collagen type I production by osteoblasts, it is not surprising that defects in many other genes have been identified that interfere with collagen type I production and cause bone fragility phenotypes. In addition, bone fragility has been associated with variants in genes that are important for osteoblast differentiation or function but that do not have

**Table 1**
Bone fragility genes and corresponding diagnoses according to the Skeletal Dysplasia Nomenclature Group [17] and the Online Mendelian Inheritance in Man (OMIM) database (https://omim.org).

| Gene | Diagnosis according to skeletal dysplasia nomenclature group | Diagnosis according to OMIM |
|---|---|---|
| Collagen type I encoding genes | | |
| *COL1A1* | OI-I, OI-II, OI-III, OI-IV | OI1, OI2, OI3, OI4 |
| *COL1A2* | OI-I, OI-II, OI-III, OI-IV | OI1, OI2, OI3, OI4 |
| Collagen type I processing | | |
| *BMP1* | OI-III | OI13 |
| *CRTAP* | OI-II, OI-III, OI-IV | OI7 |
| *FKBP10* | OI-III, OI-IV, Bruck syndrome type 1 | OI11, Bruck syndrome 1 |
| *P3H1* | OI-III | OI8 |
| *P4HB* | Cole-Carpenter Dysplasia | Cole-Carpenter syndrome 1 |
| *PLOD2* | OI-III, Bruck syndrome type 2 | Bruck syndrome 2 |
| *PPIB* | OI-II, OI-III, OI-IV | OI9 |
| *SEC24D* | OI-III | Cole-Carpenter syndrome 2 |
| *SERPINH1* | OI-III | OI10 |
| *SPARC* | NA (OI-IV) | OI17 |
| *TMEM38B* | OI-III | OI14 |
| Other osteoblast genes | | |
| *CREB3L1* | OI-III | OI16 |
| *FAM46A* | NA (OI-III, OI-IV) | OI18 |
| *IFITM5* | OI-V | OI5 |
| *LRP5* | Recessive: Osteoporosis pseudoglioma syndrome; Dominant: Primary osteoporosis | Recessive: Osteoporosis pseudoglioma syndrome |
| *MBTPS2* | NA (OI-III, OI-IV) | OI19 |
| *PLS3* | X-linked osteoporosis | X-linked osteoporosis |
| *SERPINF1* | OI-III, OI-IV | OI6 |
| *SGMS2* | NA | Calvarial doughnut lesions and osteoporosis |
| *SP7* | OI-III, OI-IV | OI12 |
| *WNT1* | OI-III, OI-IV | Recessive: OI15 Dominant: Early-onset osteoporosis |

NA: not available (genes not included in [17]). In brackets, OI types most closely corresponding to the published description of the phenotype.

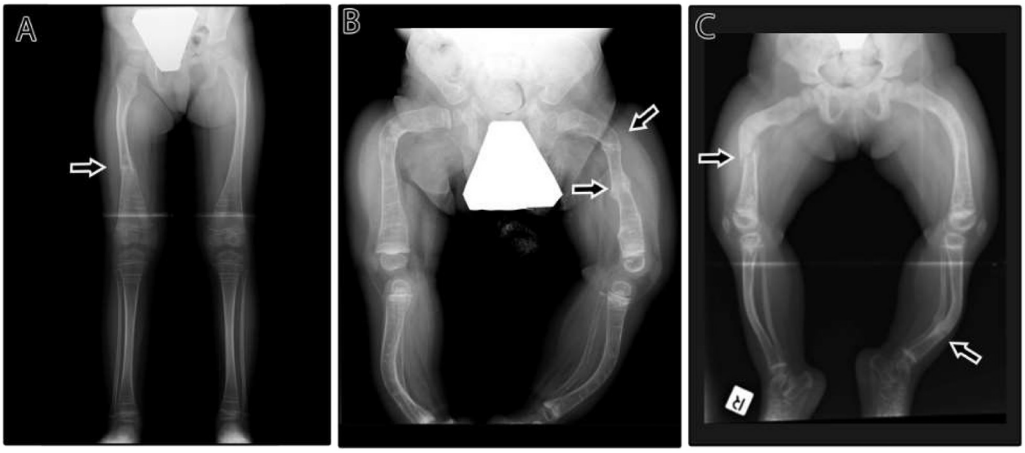


**Fig. 2.** Lower extremity radiographs in children with OI caused by mutations in *COL1A1* or *COL1A2*. (A) Three-year-old girl with mild OI caused by a stop mutation in *COL1A1*. Straight lower extremities, and fracture of the right femur (arrow). (B) Two-year-old boy with severe OI caused by a glycine substitution in *COL1A1*. Deformities of all long bones and fractures of the left femur (arrows). (C) Five-year-old girl with moderate OI caused by a glycine substitution in *COL1A2*. Long-bone deformities and fractures of the right femur and left tibia and fibula (arrows).

a known direct role in collagen type I metabolism.

The typical clinical picture of OI not only includes bone fragility but also other signs and symptoms, such as joint hyperlaxity, discoloration of the sclera and abnormalities of the teeth (dentinogenetic imperfecta) [20]. The more severe forms of OI in addition lead to deformities of long bones, the craniofacial skeleton, pelvis and spine (Fig. 2). In contrast, juvenile osteoporosis or early-onset osteoporosis are associated with fractures but not with discoloration of the sclera, dentinogenesis imperfecta or bone deformities (Fig. 3).

However, the distinction between OI and 'non-OI' bone fragility disorders is not clearly defined. On a clinical level, mutations in OI-associated genes can be present even if the phenotype is not typical for OI [21]. On a conceptual level, the classification of gene defects into OI and 'other bone fragility disorders' does not seem to follow a clear guiding principle. Many texts on OI define the disease as a disorder that is caused by abnormalities affecting collagen type I, but some of the genes that are usually classified as OI-associated genes (e.g., *IFITM5*, *SERPINF1*, *WNT1*) do not play an obvious role in collagen type I metabolism [4,22]. In contrast, defects in some other genes give rise to similar bone fragility phenotypes but are not usually considered among OI genes (e.g., *LRP5*, *PLS3*).

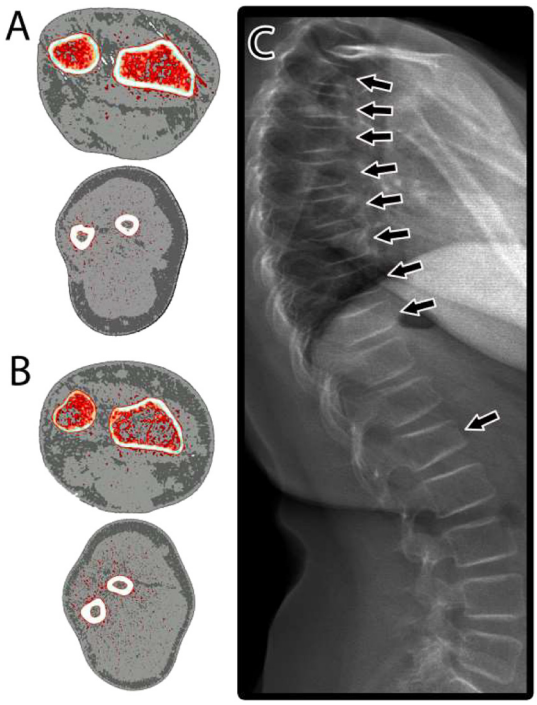


**Fig. 3.** (A) Forearm peripheral quantitative computed tomography scans at the metaphysis (upper panel) and diaphysis (lower panel) of a 41-year-old healthy woman (trabecular volumetric bone mineral density of the radius: 200 mg/cm$^3$; z-score + 0.6). (B) Corresponding scans of a 42-year-old woman with a missense variant in *LRP5* (p.Glu1094Lys; trabecular volumetric bone mineral density 111 mg/cm$^3$; z-score − 2.6). Results at the diaphysis are within normal limits. (C) Lateral spine radiograph of 7-year-old daughter of proband shown in (B), with compound heterozygous *LRP5* variants (p.Arg1036Gln and p.Glu1094Lys). Multiple vertebral compression fractures (arrows).

## 3. Pathophysiology: general features

Bone fragility disorders are commonly considered a special form of osteoporosis. In pediatrics, the diagnosis of osteoporosis is based on either the presence of both long-bone fractures and low bone densitometry results, or the presence of low-trauma vertebral fractures irrespective of bone density [23]. While monogenic bone fragility is often associated with osteoporosis thus defined, there are many exceptions. Individuals with genetic defects causing bone fragility may either not (yet) fulfill the fracture criteria for pediatric osteoporosis or may not have low bone densitometry results.

The importance of factors other than bone mass for causing bone fragility is highlighted in 'high bone mass OI' where frequent fractures occur despite normal or even slightly increased bone densitometry results [24,25]. Factors that can affect bone strength but are not necessarily reflected by bone densitometry results are abnormalities in material bone properties, trabecular microarchitecture and cortical bone geometry, all of which can be found in many individuals with OI [26–28]. For example, children with mild OI typically have diminished periosteal circumference and high bone density at long-bone diaphysis, but low bone density in trabecular bone at long-bone metaphyses and the vertebral bodies [26].

In adults, the main bone metabolic activity is bone remodeling. The slow decrease in bone mass with aging is considered an effect of remodeling with a negative balance, indicating that in each remodeling cycle osteoclasts resorb more bone than osteoblasts subsequently put back on the same bone surface [29]. During bone development, the main mechanisms driving bone accrual are bone growth in length and bone growth in circumference [30]. Bone growth in length occurs through endochondral ossification (proliferation of growth plate cartilage followed by conversion into bone tissue), whereas bone growth in circumference is achieved through modeling, in particular involving periosteal osteoblasts.

Bone growth in length and in circumference requires osteoclasts and osteoblasts and thus involve the same cell types as bone remodeling. Genetic variants that damage osteoblasts or osteoclast function should therefore affect both bone growth during development and bone loss during aging. However, the changes in bone mass and shape resulting

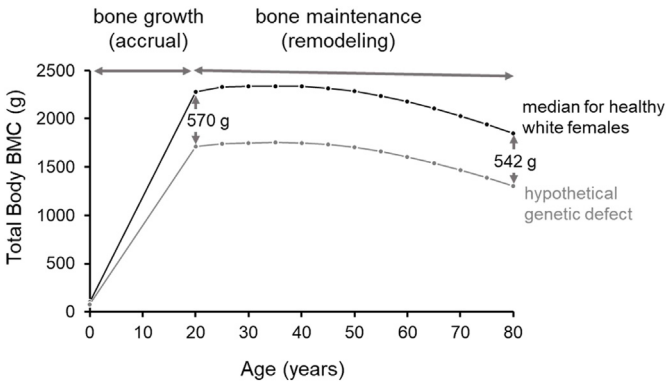


**Fig. 4.** Hypothetical model of changes in whole-body bone mineral content (BMC) with age. The black upper line corresponds to the 50th percentile of the references range for white females (39). In grey, a hypothetical curve for a genetic defect that causes a 25% BMC deficit during growth and a 25% faster percentage bone loss in each 5-year period after the age of 40 years. The absolute BMC difference changes little from 40 to 80 years of age. Even at the age of 80 years, the BMC deficit caused by the genetic defect largely results from differences in bone accrual during bone growth.

from bone growth are much larger than those resulting from bone loss during aging. It can therefore be expected that genetic variants identified as determinants of bone mass by genome wide association studies in adults will exert their effect mostly by modulating bone growth rather than bone remodeling (Fig. 4).

## 4. Bone fragility caused by disturbances in collagen type I

### 4.1. *COL1A1 and COL1A2*

About 1 in 10,000 individuals have a clinical diagnosis of OI, making this the most commonly recognized monogenic bone fragility disorder. It has been known for more than three decades that the large majority of individuals with an OI phenotype have disease-causing dominant variants in *COL1A1* or *COL1A2* [31].

Collagen type I consists of two alpha 1 chains, encoded by *COL1A1*, and one alpha 2 chain, encoded by *COL1A2*. The main domains of the collagen type I molecule are the N-propeptide, the triple-helical domain, and the C-propeptide [18]. After osteoblasts secrete collagen type I, the N- and C-propeptides are cleaved off and removed through the systemic circulation; the triple-helical domain is integrated into collagen fibrils, a key constituent of the extracellular bone matrix. In the triple helical domain the collagen type I alpha 1 and alpha 2 chains are intertwined in a very regular pattern that is contingent on the presence of a glycine residue at every third position in both alpha chains.

Two broad classes of genetic defects are the most common cause of OI, namely variants that lead to a quantitative collagen defect and variants that lead to a qualitative collagen defect. Quantitative defects are caused by null mutations in *COL1A1* (typically nonsense or frameshift mutations), leading to haploinsufficiency in the alpha 1 chain. Null mutations in *COL1A2* do not lead to OI, presumably because half as many alpha 2 than alpha 1 chains are needed for collagen type I production and therefore it is possible to compensate for a non-functional *COL1A2*.

*COL1A1* haploinsufficiency mutations consistently lead to mild OI that is characterized by bone fragility but absence of bone deformities [32]. Sclera usually have a grey or blue hue. Even though *COL1A1* haploinsufficiency represents the mildest form of OI, fracture risk is substantially increased compared to the general population. A hospital-based study on patients with *COL1A1* haploinsufficiency mutations found that 70% of these individuals had vertebral fractures in the first two decades of life and that the incidence of femur and tibia fractures in these children and adolescents was 90-fold higher than that of the age- and sex-matched general population [7].

Qualitative collagen defects are most commonly caused by glycine substitutions in the triple-helical domain of either the alpha 1 or the alpha 2 chain. Glycine is the smallest amino acid and is required on every third position of both alpha chains for the triple helical to fold properly. Substitution of these glycine residues by any other amino acid creates steric hindrance in the folding of the alpha chains and therefore interferes with the formation of the triple helix. The degree to which a glycine substitution is detrimental to the collagen type I molecule depends on which glycine residue in which chain is affected, and by which amino acid the glycine residue is replaced. In general, substitutions of a given glycine residue by a large or charged amino acid (such as aspartate, arginine or lysine) is more detrimental than substitution by a smaller amino acid. Triple-helical glycine substitutions therefore can give rise to the entire phenotypic breadth of OI, from very mild forms to lethal OI. One study found that untreated individuals with OI who were assessed in a pediatric orthopedic institution and who had glycine substitution mutations in either *COL1A1* or *COL1A2* had a mean lumbar spine areal bone mineral density z-score of about −5, with a large interindividual variability, from −0.8 to −7.8 [33].

### 4.2. *Genes involved in collagen type I metabolism*

After translation, collagen type I alpha 1 and alpha 2 chains undergo extensive posttranslational modifications and assembly into collagen type I molecules in the endoplasmic reticulum, transport to the Golgi, secretion into the extracellular space, assembly of collagen fibrils and cross-linking [18]. A large number of enzymes, co-factors and transport molecules participate in this process and pathogenic variants in several genes coding for these proteins are known to cause an OI phenotype (Table 1). All of these variants are very rare; cumulatively they are found in about 5% of individuals with moderate to severe OI [19]. Mutations in these genes usually give rise to recessive OI, and heterozygous carriers do not have a detectable phenotype. The exception is a mutation in *P4HB* that causes a dominant bone fragility syndrome [34].

### 4.3. *Implications for adult osteoporosis*

Although the typical phenotype caused by *COL1A1* and *COL1A2* mutations is readily recognized on clinical examination, it is likely that many individuals with milder but still damaging variants in *COL1A1* or *COL1A2* are not diagnosed with OI. Extraskeletal signs of OI, such as scleral discoloration or dentinogenesis imperfecta, are not present in all individuals with OI, which makes the clinical diagnosis of mild OI more difficult [21]. Such individuals can present as having pregnancy-associated osteoporosis [35], may be diagnosed in osteoporosis clinics as older adults [36–38] or are sometimes identified only when their children sustain fractures and are assessed for OI (own observation).

Missense mutations in *COL1A1* or *COL1A2* affecting glycine residues at the Gly-X-Y position in the triple helical domain, mutations leading to premature stop codons in *COL1A1*, or *COL1A1* splice site mutations are expected to lead to OI [39]. Nevertheless, large-scale sequencing efforts suggest that such mutations are much more common in the general population than the prevalence of OI would suggest. The allele frequency of such *COL1A1* or *COL1A2* mutations in gnomAD, a database that contains whole-exome or whole-genome sequencing results from more than 140,000 adults not diagnosed with any severe pediatric disorder (https://gnomad.broadinstitute.org/), is 0.018% for *COL1A1* (Table 2) and 0.032% for *COL1A2* (Table 3). Some of these variants have previously been observed in individuals with OI. The combined allele frequency of these *COL1A1/COL1A2* mutations (0.05%) indicates that 0.1% of individuals in this database carry a variant that should lead to OI. This is 10 times more frequent than the population prevalence of OI (0.01%). Thus, it can be surmised that 90% of carriers of putative 'OI mutations' do not have a diagnosis of OI. It appears plausible that many of these individuals have a partial OI phenotype that resembles adult

**Table 2**
Heterozygous *COL1A1* variants in the gnomAD database that are predicted to cause OI. The cumulative allele frequency of these variants is 0.018%.

| Transcript consequence | Protein consequence | Allele frequency | In OI variant database[a] |
|---|---|---|---|
| Triple-helical glycine substitutions at the Gly-X-Y position | | | |
| c.545G > T | p.Gly182Val | 7.98E-06 | n |
| c.554G > T | p.Gly185Val | 3.99E-06 | n |
| c.2210G > C | p.Gly737Ala | 3.19E-05 | n |
| c.2273G > C | p.Gly758Ala | 3.19E-05 | n |
| c.3101G > A | p.Gly1034Asp | 3.99E-06 | n |
| c.3469G > A | p.Gly1157Ser | 8.06E-06 | n |
| Haploinsufficiency or splice defects | | | |
| c.253dupG | p.Glu85GlyfsTer84 | 3.99E-06 | n |
| c.903 + 1G > A | | 3.98E-06 | y |
| c.1008delC | p.Thr337ProfsTer204 | 4.66E-06 | n |
| c.1056 + 2T > C | | 3.54E-05 | n |
| c.1792C > T | p.Arg598Ter | 4E-06 | y |
| c.1876-1G > A | | 3.98E-06 | n |
| c.2073delT | p.Gly692ValfsTer74 | 4.32E-06 | y |
| c.2089C > T | p.Arg697Ter | 3.19E-05 | y |

[a] Web address: https://www.le.ac.uk/ge/collagen/.

**Table 3**
Heterozygous *COL1A2* variants in the gnomAD database that are predicted to cause OI. All variants are predicted to lead to glycine substitutions at the Gly-X-Y position in the triple-helical domain. The cumulative allele frequency of these variants is 0.032%.

| Transcript consequence | Protein consequence | Allele frequency | In OI variant database[a] |
|---|---|---|---|
| c.271G > A | p.Gly91Arg | 4.00E-06 | n |
| c.298G > A | p.Gly100Ser | 7.07E-06 | n |
| c.316G > A | p.Gly106Arg | 3.98E-06 | n |
| c.352G > A | p.Gly118Ser | 3.98E-06 | n |
| c.451G > A | p.Gly151Arg | 3.98E-06 | n |
| c.487G > A | p.Gly163Ser | 3.98E-06 | n |
| c.515G > T | p.Gly172Val | 3.98E-06 | n |
| c.533G > A | p.Gly178Asp | 3.98E-06 | n |
| c.577G > A | p.Gly193Ser | 3.98E-06 | y |
| c.613G > A | p.Gly205Ser | 3.19E-05 | n |
| c.614G > C | p.Gly205Ala | 3.98E-06 | n |
| c.658G > A | p.Gly220Ser | 3.98E-06 | n |
| c.659G > C | p.Gly220Ala | 3.98E-06 | n |
| c.668G > A | p.Gly223Glu | 1.19E-05 | n |
| c.694G > A | p.Gly232Ser | 3.98E-06 | n |
| c.713G > A | p.Gly238Glu | 3.98E-06 | n |
| c.793G > A | p.Gly265Ser | 3.18E-05 | n |
| c.830G > C | p.Gly277Ala | 1.19E-05 | n |
| c.838G > A | p.Gly280Ser | 7.95E-06 | y |
| c.1199G > C | p.Gly400Ala | 3.98E-06 | n |
| c.1423G > A | p.Gly475Ser | 3.99E-06 | n |
| c.1522G > A | p.Gly508Ser | 7.95E-06 | n |
| c.1874G > C | p.Gly625Ala | 4.59E-06 | n |
| c.2027G > C | p.Gly676Ala | 3.98E-06 | n |
| c.2071G > C | p.Gly691Arg | 3.19E-05 | n |
| c.2251G > A | p.Gly751Ser | 4.07E-06 | y |
| c.2701G > A | p.Gly901Ser | 3.98E-06 | y |
| c.2711G > C | p.Gly904Ala | 1.99E-05 | n |
| c.2755G > A | p.Gly919Ser | 3.98E-05 | y |
| c.2755G > C | p.Gly919Arg | 3.98E-06 | n |
| c.2881G > A | p.Gly961Ser | 4.03E-06 | n |
| c.2882G > T | p.Gly961Val | 8.06E-06 | n |
| c.2908G > A | p.Gly970Ser | 4.06E-06 | n |
| c.3142G > A | p.Gly1048Ser | 3.98E-06 | n |
| c.3187G > A | p.Gly1063Arg | 3.99E-06 | n |
| c.3196G > A | p.Gly1066Ser | 3.99E-06 | n |
| c.3241G > A | p.Gly1081Ser | 8.01E-06 | n |
| c.3305G > A | p.Gly1102Asp | 3.98E-06 | y |

[a] Web address: https://www.le.ac.uk/ge/collagen/.

osteoporosis.

An example for this scenario are two *COL1A2* glycine substitutions (p.Gly496Ala and p.Gly703Ser) that were identified in a large whole-genome sequencing study in Iceland [40]. These variants had a combined allelic frequency of 0.15% in this population and were associated with low bone mineral density, fractures and a slightly below-average height, but not with other clinical features of OI such as dentinogenesis imperfecta or blue/grey sclera. Similarly, a case report of a Greek family suggested that some glycine substitutions caused by *COL1A2* mutations can have such mild effects that they do not cause a detectable phenotype in heterozygous individuals, but lead to OI when homozygous [41]. Glycine substitutions in *COL1A2* have also been reported in adults who were assessed for early onset osteoporosis but who were not thought to have OI prior to genetic testing [38].

## 5. Bone fragility caused by variants in other osteoblast genes

Variants in genes involved in a variety of osteoblast/osteocyte functions other than collagen type I production or variants in genes that are expressed in the osteoblast lineage but do not have a well-characterized function can also cause Mendelian bone fragility disorders. *LRP5* and *WNT1* are the most frequently studied genes in this category, as they are key components of the WNT signaling pathway, which has a major importance for bone development and maintenance [42]. Variants in or close to *LRP5* are consistently identified by GWAS studies as a determinant of bone density and fractures [43,44].

It has been known for almost two decades that bi-allelic loss of function mutations in *LRP5* cause osteoporosis-pseudoglioma syndrome, a disorder that is characterized by ocular manifestations in addition to severe bone fragility [45]. It was noted at the same time that heterozygous parents of individuals with osteoporosis-pseudoglioma syndrome have low bone mineral density and increased fracture risk [45]. Heterozygous loss of function mutations in *LRP5* were later also identified as a cause of osteoporosis and fractures in children and young adults [21,38,46]. In vitro assays have demonstrated that such mutations decrease the activity of WNT signaling [38,46].

*WNT1* has long been regarded as a gene that is essential for brain development, as the Wnt1 deficient mouse has severe brain abnormalities [47]. However, humans with biallelic loss of function mutations in *WNT1* consistently have severe bone fragility and only some of these individuals seem to have structural brain abnormalities [48–50]. Heterozygous family members of individuals with severe bone fragility caused by homozygous *WNT1* mutations have low bone mineral density and mild bone fragility [48,51,52]. WNT1 seems to control the activity of bone formation in osteoblasts mainly through its action in osteocytes [53].

Inactivating *PLS3* mutations cause an X-linked form of monogenic bone fragility that usually causes more severe clinical manifestations in hemizygous males than in heterozygous females [54]. *PLS3* is highly expressed in cells of the osteoblast lineage and is thought to be involved in mechanosensing [54,55]. There is also evidence that plastin 3, the protein encoded by *PLS3*, plays a role in osteoclasts [56].

Other genes associated with monogenic bone fragility code for transcription factors (*SP7* [57]), proteins that are involved in the osteoblast stress response (*CREB3L1*, *MBTPS2* [58]), enzymes regulating sphingomyelin metabolism (*SGMS2* [59]) and proteins that do not have a well-characterized function (*IFITM5* [60], *FAM46A* [61]).

### 5.1. Implications for adult osteoporosis

It is conceivable that rare variants in *LRP5* and *WNT1* cumulatively are a relatively frequent cause of monogenic bone fragility. The gnomAD database lists more than 700 rare variants (allele frequency of 0.2% or lower) in *LRP5* and more than 130 rare variants in *WNT1* that are only observed in heterozygous fashion and that lead to premature termination codons or amino acid substitutions. The cumulative allele

frequency of these rare *LRP5* and *WNT1* variants is about 2.4%, indicating that close to 5% of the apparently healthy adult study participants are carriers of such variants. Several of the listed *LRP5* and *WNT1* missense variants have been demonstrated to decrease WNT signaling by in vitro testing [38,46,50]. Thus, even if only a portion of these *LRP5* and *WNT1* variants give rise to monogenic bone fragility, such variants could make a substantial contribution to fracture incidence in the population.

## 6. Conclusions

Genetic studies on Mendelian bone fragility disorders in the past have mainly focussed on situations with high fracture rates during childhood and that gave rise to an OI phenotype. As almost all individuals with a typical OI phenotype now have a detectable variant in one of the known OI-associated genes, new causes of monogenic bone fragility are therefore more likely to be discovered by studying individuals who do not have a typical OI phenotype. Conversely, evidence is emerging that what appears as primary osteoporosis based on clinical appearance in fact can be due to mutations in bona fide OI genes. As sequencing studies are more widely performed in individuals with milder bone fragility phenotypes, the distinction between OI and primary osteoporosis is likely to blur further.

## Disclosures

The authors state that they have the following disclosures:
Marie-Eve Robinson: None.
Frank Rauch: PreciThera Inc. (study grant).

## Acknowledgments

This work was supported by the Shriners of North America.

## References

[1] R.J. Moon, N.C. Harvey, E.M. Curtis, F. de Vries, T. van Staa, C. Cooper, Ethnic and geographic variations in the epidemiology of childhood fractures in the United Kingdom, Bone 85 (2016) 9–14.
[2] F. Rauch, C. Neu, F. Manz, E. Schoenau, The development of metaphyseal cortex–implications for distal radius fractures during growth, J. Bone Miner. Res. 16 (2001) 1547–1555.
[3] K.Y. Cheuk, X.F. Wang, J. Wang, Z. Zhang, F.W.P. Yu, E.M.S. Tam, V.W.Y. Hung, W.Y.W. Lee, A. Ghasem-Zadeh, R. Zebaze, T.Y. Zhu, X.E. Guo, J.C.Y. Cheng, T.P. Lam, E. Seeman, Sexual dimorphism in cortical and trabecular bone microstructure appears during puberty in chinese children, J. Bone Miner. Res. 33 (2018) 1948–1955.
[4] R.E. Makitie, A. Costantini, A. Kampe, J.J. Alm, O. Makitie, New insights into monogenic causes of osteoporosis, Front. Endocrinol. (Lausanne) 10 (2019) 70.
[5] L. Folkestad, J.D. Hald, A.K. Ersboll, J. Gram, A.P. Hermann, B. Langdahl, B. Abrahamsen, K. Brixen, Fracture rates and fracture sites in patients with osteogenesis imperfecta: a nationwide register-based cohort study, J. Bone Miner. Res. 32 (2017) 125–134.
[6] K. Trajanoska, J.A. Morris, L. Oei, H.F. Zheng, D.M. Evans, D.P. Kiel, C. Ohlsson, J.B. Richards, F. Rivadeneira, Assessment of the genetic and clinical determinants of fracture risk: genome wide association and mendelian randomisation study, Bmj 362 (2018) k3225.
[7] I.M. Ben Amor, P. Roughley, F.H. Glorieux, F. Rauch, Skeletal clinical characteristics of osteogenesis imperfecta caused by haploinsufficiency mutations in COL1A1, J. Bone Miner. Res. 28 (2013) 2001–2007.
[8] S. Bellur, M. Jain, D. Cuthbertson, D. Krakow, J.R. Shapiro, R.D. Steiner, P.A. Smith, M.B. Bober, T. Hart, J. Krischer, M. Mullins, P.H. Byers, M. Pepin, M. Durigova, F.H. Glorieux, F. Rauch, V.R. Sutton, B. Lee, S.C. Nagamani, Cesarean delivery is not associated with decreased at-birth fracture rates in osteogenesis imperfecta, Genet. Med. 18 (2016) 570–576.
[9] S. Sakka, R.I. Gafni, J.H. Davies, B. Clarke, P. Tebben, M. Samuels, V. Saraff, K. Klaushofer, N. Fratzl-Zelman, P. Roschger, F. Rauch, W. Hogler, Bone structural characteristics and response to bisphosphonate treatment in children with Hajdu-Cheney syndrome, J. Clin. Endocrinol. Metab. 102 (2017) 4163–4172.
[10] S.C. Cooper, C.M. Flaitz, D.A. Johnston, B. Lee, J.T. Hecht, A natural history of cleidocranial dysplasia, Am. J. Med. Genet. 104 (2001) 1–6.
[11] P. Moffatt, M. Ben Amor, F.H. Glorieux, P. Roschger, K. Klaushofer, J.A. Schwartzentruber, A.D. Paterson, P. Hu, C. Marshall, S. Fahiminiya, J. Majewski, C.L. Beaulieu, K.M. Boycott, F. Rauch, Rauch is caused by a duplication in RUNX2, Am. J. Hum. Genet. 92 (2013) 252–258.
[12] A. Teti, M.J. Econs, Osteopetroses, emphasizing potential approaches to treatment, Bone 102 (2017) 50–59.
[13] D.J. Birnkrant, K. Bushby, C.M. Bann, B.A. Alman, S.D. Apkon, A. Blackwell, L.E. Case, L. Cripe, S. Hadjiyannakis, A.K. Olson, D.W. Sheehan, J. Bolen, D.R. Weber, L.M. Ward, Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management, Lancet Neurol. 17 (2018) 347–361.
[14] S. Vai, M.L. Bianchi, I. Moroni, C. Mastella, F. Broggi, L. Morandi, M.T. Arnoldi, C. Bussolino, G. Baranello, Bone and spinal muscular atrophy, Bone 79 (2015) 116–120.
[15] H.N. Baris, I.J. Cohen, P.K. Mistry, Gaucher disease: the metabolic defect, pathophysiology, phenotypes and natural history, Pediatr. Endocrinol. Rev. 12 (Suppl. 1) (2014) 72–81.
[16] L.M. Ward, V.N. Konji, J. Ma, The management of osteoporosis in children, Osteoporos. Int. 27 (2016) 2147–2179.
[17] L. Bonafe, V. Cormier-Daire, C. Hall, R. Lachman, G. Mortier, S. Mundlos, G. Nishimura, L. Sangiorgi, R. Savarirayan, D. Sillence, J. Spranger, A. Superti-Furga, M. Warman, S. Unger, Nosology and classification of genetic skeletal disorders: 2015 revision, Am. J. Med. Genet. A 167A (2015) 2869–2892.
[18] A. Forlino, J.C. Marini, Osteogenesis imperfecta, Lancet 387 (2016) 1657–1671.
[19] G. Bardai, P. Moffatt, F.H. Glorieux, F. Rauch, DNA sequence analysis in 598 individuals with a clinical diagnosis of osteogenesis imperfecta: diagnostic yield and mutation spectrum, Osteoporos. Int. 27 (2016) 3607–3613.
[20] P. Trejo, F. Rauch, Osteogenesis imperfecta in children and adolescents-new developments in diagnosis and treatment, Osteoporos. Int. 27 (2016) 3427–3437.
[21] G. Bardai, L.M. Ward, P. Trejo, P. Moffatt, F.H. Glorieux, F. Rauch, Molecular diagnosis in children with fractures but no extraskeletal signs of osteogenesis imperfecta, Osteoporos. Int. 28 (2017) 2095–2101.
[22] F. Rivadeneira, O. Makitie, Osteoporosis and bone mass disorders: from gene pathways to treatments, Trends Endocrinol. Metab. 27 (2016) 262–281.
[23] N. Bishop, P. Arundel, E. Clark, P. Dimitri, J. Farr, G. Jones, O. Makitie, C.F. Munns, N. Shaw, Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 pediatric official positions, J. Clin. Densitom. 17 (2014) 275–280.
[24] Cundy T, Dray M, Delahunt J, Hald JD, Langdahl B, Li C, Szybowska M, Mohammed S, Duncan EL, McInerney-Leo AM, Wheeler PG, Roschger P, Klaushofer K, Rai J, Weis M, Eyre D, Schwarze U, Byers PH, Mutations that alter the carboxy-terminal-propeptide cleavage site of the chains of type I procollagen are associated with a unique osteogenesis imperfecta phenotype, J. Bone Miner. Res. 33 (2018) 1260–1271.
[25] S. Fahiminiya, H. Al-Jallad, J. Majewski, T. Palomo, P. Moffatt, P. Roschger, K. Klaushofer, F.H. Glorieux, F. Rauch, A polyadenylation site variant causes transcript-specific BMP1 deficiency and frequent fractures in children, Hum. Mol. Genet. 24 (2015) 516–524.
[26] F. Rauch, C. Land, S. Cornibert, E. Schoenau, F.H. Glorieux, High and low density in the same bone: a study on children and adolescents with mild osteogenesis imperfecta, Bone 37 (2005) 634–641.
[27] P. Roschger, N. Fratzl-Zelman, B.M. Misof, F.H. Glorieux, K. Klaushofer, F. Rauch, Evidence that abnormal high bone mineralization in growing children with osteogenesis imperfecta is not associated with specific collagen mutations, Calcif. Tissue Int. 82 (2008) 263–270.
[28] J.D. Hald, L. Folkestad, T. Harslof, A.M. Lund, M. Duno, J.B. Jensen, S. Neghabat, K. Brixen, B. Langdahl, Skeletal phenotypes in adult patients with osteogenesis imperfecta-correlations with COL1A1/COL1A2 genotype and collagen structure, Osteoporos. Int. 27 (2016) 3331–3341.
[29] E. Seeman, Pathogenesis of bone fragility in women and men, Lancet 359 (2002) 1841–1850.
[30] Rauch F. the dynamics of bone structure development during pubertal growth, J. Musculoskelet. Neuronal Interact. 12 (2012) 1–6.
[31] B. Sykes, D. Ogilvie, P. Wordsworth, G. Wallis, C. Mathew, P. Beighton, A. Nicholls, F.M. Pope, E. Thompson, P. Tsipouras, Consistent linkage of dominantly inherited osteogenesis imperfecta to the type I collagen loci: COL1A1 and COL1A2, Am. J. Hum. Genet. 46 (1990) 293–307.
[32] J.T. Tauer, M.-E. Robinson, F. Rauch, Osteogenesis imperfecta: new perspectives from clinical and translational research, JBMR Plus (2019), https://doi.org/10.1002/jbm4.10174.
[33] F. Rauch, L. Lalic, P. Roughley, F.H. Glorieux, Relationship between genotype and skeletal phenotype in children and adolescents with osteogenesis imperfecta, J. Bone Miner. Res. 25 (2010) 1367–1374.
[34] F. Rauch, S. Fahiminiya, J. Majewski, J. Carrot-Zhang, S. Boudko, F. Glorieux, J.S. Mort, H.P. Bachinger, P. Moffatt, Cole-carpenter syndrome is caused by a heterozygous missense mutation in P4HB, Am. J. Hum. Genet. 96 (2015) 425–431.
[35] S. Butscheidt, A. Delsmann, T. Rolvien, F. Barvencik, M. Al-Bughaili, S. Mundlos, T. Schinke, M. Amling, U. Kornak, R. Oheim, Mutational analysis uncovers monogenic bone disorders in women with pregnancy-associated osteoporosis: three novel mutations in LRP5, COL1A1, and COL1A2, Osteoporos. Int. 29 (2018) 1643–1651.
[36] S. Lampart, S. Azzarello-Burri, C. Henzen, S. Fischli, Special form of osteoporosis in a 53-year-old man, BMJ Case Rep. 11 (2018).
[37] T. Rolvien, J. Sturznickel, F.N. Schmidt, S. Butscheidt, T. Schmidt, B. Busse, S. Mundlos, T. Schinke, U. Kornak, M. Amling, R. Oheim, Comparison of bone microarchitecture between adult osteogenesis imperfecta and early-onset osteoporosis, Calcif. Tissue Int. 103 (2018) 512–521.
[38] C. Collet, A. Ostertag, M. Ricquebourg, M. Delecourt, G. Tueur, B. Isidor, P. Guillot, E. Schaefer, R.M. Javier, T. Funck-Brentano, P. Orcel, J.L. Laplanche, M. Cohen-Solal, Primary osteoporosis in young adults: genetic basis and identification of novel variants in causal genes, JBMR Plus 2 (2018) 12–21.

[39] J.C. Marini, A. Forlino, W.A. Cabral, A.M. Barnes, J.D. San Antonio, S. Milgrom, J.C. Hyland, J. Korkko, D.J. Prockop, A. De Paepe, P. Coucke, S. Symoens, F.H. Glorieux, P.J. Roughley, A.M. Lund, K. Kuurila-Svahn, H. Hartikka, D.H. Cohn, D. Krakow, M. Mottes, U. Schwarze, D. Chen, K. Yang, C. Kuslich, J. Troendle, R. Dalgleish, P.H. Byers, Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans, Hum. Mutat. 28 (2007) 209–221.

[40] U. Styrkarsdottir, G. Thorleifsson, B. Eiriksdottir, S.A. Gudjonsson, T. Ingvarsson, J.R. Center, T.V. Nguyen, J.A. Eisman, C. Christiansen, U. Thorsteinsdottir, G. Sigurdsson, K. Stefansson, Two rare mutations in the COL1A2 gene associate with low bone mineral density and fractures in Iceland, J. Bone Miner. Res. 31 (2016) 173–179.

[41] A. Costantini, S. Tournis, A. Kampe, N. Ul Ain, F. Taylan, A. Doulgeraki, O. Makitie, Autosomal recessive osteogenesis imperfecta caused by a novel homozygous COL1A2 mutation, Calcif. Tissue Int. 103 (2018) 353–358.

[42] R. Nusse, H. Clevers, Wnt/beta-catenin signaling, disease, and emerging therapeutic modalities, Cell 169 (2017) 985–999.

[43] J.A. Morris, J.P. Kemp, S.E. Youlten, L. Laurent, J.G. Logan, R.C. Chai, N.A. Vulpescu, V. Forgetta, A. Kleinman, S.T. Mohanty, C.M. Sergio, J. Quinn, L. Nguyen-Yamamoto, A.L. Luco, J. Vijay, M.M. Simon, A. Pramatarova, C. Medina-Gomez, K. Trajanoska, E.J. Ghirardello, N.C. Butterfield, K.F. Curry, V.D. Leitch, P.C. Sparkes, A.T. Adoum, N.S. Mannan, D.S.K. Komla-Ebri, A.S. Pollard, H.F. Dewhurst, T.A.D. Hassall, M.G. Beltejar, D.J. Adams, S.M. Vaillancourt, S. Kaptoge, P. Baldock, C. Cooper, J. Reeve, E.E. Ntzani, E. Evangelou, C. Ohlsson, D. Karasik, F. Rivadeneira, D.P. Kiel, J.H. Tobias, C.L. Gregson, N.C. Harvey, E. Grundberg, D. Goltzman, D.J. Adams, C.J. Lelliott, D.A. Hinds, C.L. Ackert-Bicknell, Y.H. Hsu, M.T. Maurano, P.I. Croucher, G.R. Williams, J.H.D. Bassett, D.M. Evans, J.B. Richards, An atlas of genetic influences on osteoporosis in humans and mice, Nat. Genet. 51 (2019) 258–266.

[44] K. Trajanoska, J.D. Schoufour, E.A.L. de Jonge, B.C.T. Kieboom, M. Mulder, B.H. Stricker, T. Voortman, A.G. Uitterlinden, E.H.G. Oei, M. Arfan Ikram, M. Carola Zillikens, F. Rivadeneira, L. Oei, Fracture incidence and secular trends between 1989 and 2013 in a population based cohort: the Rotterdam study, Bone 114 (2018) 116–124.

[45] Y. Gong, R.B. Slee, N. Fukai, G. Rawadi, S. Roman-Roman, A.M. Reginato, H. Wang, T. Cundy, F.H. Glorieux, D. Lev, M. Zacharin, K. Oexle, J. Marcelino, W. Suwairi, S. Heeger, G. Sabatakos, S. Apte, W.N. Adkins, J. Allgrove, M. Arslan-Kirchner, J.A. Batch, P. Beighton, G.C. Black, R.G. Boles, L.M. Boon, C. Borrone, H.G. Brunner, G.F. Carle, B. Dallapiccola, A. De Paepe, B. Floege, M.L. Halfhide, B. Hall, R.C. Hennekam, T. Hirose, A. Jans, H. Juppner, C.A. Kim, K. Keppler-Noreuil, A. Kohlschuetter, D. LaCombe, M. Lambert, E. Lemyre, T. Letteboer, L. Peltonen, R.S. Ramesar, M. Romanengo, H. Somer, E. Steichen-Gersdorf, B. Steinmann, B. Sullivan, A. Superti-Furga, W. Swoboda, M.J. van den Boogaard, W. Van Hul, M. Vikkula, M. Votruba, B. Zabel, T. Garcia, R. Baron, B.R. Olsen, M.L. Warman, LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development, Cell 107 (2001) 513–523.

[46] J. Korvala, H. Juppner, O. Makitie, E. Sochett, D. Schnabel, S. Mora, C.F. Bartels, M.L. Warman, D. Deraska, W.G. Cole, H. Hartikka, L. Ala-Kokko, M. Mannikko, Mutations in LRP5 cause primary osteoporosis without features of OI by reducing Wnt signaling activity, BMC Med. Genet. 13 (2012) 26.

[47] K.R. Thomas, M.R. Capecchi, Targeted disruption of the murine int-1 proto-oncogene resulting in severe abnormalities in midbrain and cerebellar development, Nature 346 (1990) 847–850.

[48] C.M. Laine, K.S. Joeng, P.M. Campeau, R. Kiviranta, K. Tarkkonen, M. Grover, J.T. Lu, M. Pekkinen, M. Wessman, T.J. Heino, V. Nieminen-Pihala, M. Aronen, T. Laine, H. Kroger, W.G. Cole, A.E. Lehesjoki, L. Nevarez, D. Krakow, C.J. Curry, D.H. Cohn, R.A. Gibbs, B.H. Lee, O. Makitie, WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta, N. Engl. J. Med. 368 (2013) 1809–1816.

[49] K.A. Aldinger, N.J. Mendelsohn, B.H. Chung, W. Zhang, D.H. Cohn, B. Fernandez, F.S. Alkuraya, W.B. Dobyns, C.J. Curry, Variable brain phenotype primarily affects the brainstem and cerebellum in patients with osteogenesis imperfecta caused by recessive WNT1 mutations, J. Med. Genet. 53 (2016) 427–430.

[50] Y. Lu, X. Ren, Y. Wang, G. Bardai, M. Sturm, Y. Dai, O. Riess, Y. Zhang, H. Li, T. Li, N. Zhai, J. Zhang, F. Rauch, J. Han, Novel WNT1 mutations in children with osteogenesis imperfecta: clinical and functional characterization, Bone 114 (2018) 144–149.

[51] K. Keupp, F. Beleggia, H. Kayserili, A.M. Barnes, M. Steiner, O. Semler, B. Fischer, G. Yigit, C.Y. Janda, J. Becker, S. Breer, U. Altunoglu, J. Grunhagen, P. Krawitz, J. Hecht, T. Schinke, E. Makareeva, E. Lausch, T. Cankaya, J.A. Caparros-Martin, P. Lapunzina, S. Temtamy, M. Aglan, B. Zabel, P. Eysel, F. Koerber, S. Leikin, K.C. Garcia, C. Netzer, E. Schonau, V.L. Ruiz-Perez, S. Mundlos, M. Amling, U. Kornak, J. Marini, B. Wollnik, Mutations in WNT1 cause different forms of bone fragility, Am. J. Hum. Genet. 92 (2013) 565–574.

[52] T. Palomo, H. Al-Jallad, P. Moffatt, F.H. Glorieux, B. Lentle, P. Roschger, K. Klaushofer, F. Rauch, Skeletal characteristics associated with homozygous and heterozygous WNT1 mutations, Bone 67 (2014) 63–70.

[53] K.S. Joeng, Y.C. Lee, J. Lim, Y. Chen, M.M. Jiang, E. Munivez, C. Ambrose, B.H. Lee, Osteocyte-specific WNT1 regulates osteoblast function during bone homeostasis, J. Clin. Invest. 127 (2017) 2678–2688.

[54] F.S. van Dijk, M.C. Zillikens, D. Micha, M. Riessland, C.L. Marcelis, C.E. de Die-Smulders, J. Milbradt, A.A. Franken, A.J. Harsevoort, K.D. Lichtenbelt, H.E. Pruijs, M.E. Rubio-Gozalbo, R. Zwertbroek, Y. Moutaouakil, J. Egthuijsen, M. Hammerschmidt, R. Bijman, C.M. Semeins, A.D. Bakker, V. Everts, J. Klein-Nulend, N. Campos-Obando, A. Hofman, G.J. te Meerman, A.J. Verkerk, A.G. Uitterlinden, A. Maugeri, E.A. Sistermans, Q. Waisfisz, H. Meijers-Heijboer, B. Wirth, M.E. Simon, G. Pals, PLS3 mutations in X-linked osteoporosis with fractures, N. Engl. J. Med. 369 (2013) 1529–1536.

[55] S. Fahiminiya, J. Majewski, H. Al-Jallad, P. Moffatt, J. Mort, F.H. Glorieux, P. Roschger, K. Klaushofer, F. Rauch, Osteoporosis caused by mutations in PLS3: clinical and bone tissue characteristics, J. Bone Miner. Res. 29 (2014) 1805–1814.

[56] J. Neugebauer, J. Heilig, S. Hosseinibarkooie, B.C. Ross, N. Mendoza-Ferreira, F. Nolte, M. Peters, I. Holker, K. Hupperich, T. Tschanz, V. Grysko, F. Zaucke, A. Niehoff, B. Wirth, Plastin 3 influences bone homeostasis through regulation of osteoclast activity, Hum. Mol. Genet. 27 (2018) 4249–4262.

[57] M. Fiscaletti, A. Biggin, B. Bennetts, K. Wong, J. Briody, V. Pacey, C. Birman, C.F. Munns, Novel variant in Sp7/Osx associated with recessive osteogenesis imperfecta with bone fragility and hearing impairment, Bone 110 (2018) 66–75.

[58] U. Lindert, W.A. Cabral, S. Ausavarat, S. Tongkobpetch, K. Ludin, A.M. Barnes, P. Yeetong, M. Weis, B. Krabichler, C. Srichomthong, E.N. Makareeva, A.R. Janecke, S. Leikin, B. Rothlisberger, M. Rohrbach, I. Kennerknecht, D.R. Eyre, K. Suphapeetiporn, C. Giunta, J.C. Marini, V. Shotelersuk, MBTPS2 mutations cause defective regulated intramembrane proteolysis in X-linked osteogenesis imperfecta, Nat. Commun. 7 (2016) 11920.

[59] M. Pekkinen, P.A. Terhal, L.D. Botto, P. Henning, R.E. Makitie, P. Roschger, A. Jain, M. Kol, M.A. Kjellberg, E.P. Paschalis, K. van Gassen, M. Murray, P. Bayrak-Toydemir, M.K. Magnusson, J. Jans, M. Kausar, J.C. Carey, P. Somerharju, U.H. Lerner, O.M. Vesa, K. Klaushofer, J.C. Holthuis, O. Makitie, Osteoporosis and skeletal dysplasia caused by pathogenic variants in SGMS2, JCI Insight 4 (2019) 1–20.

[60] O. Semler, L. Garbes, K. Keupp, D. Swan, K. Zimmermann, J. Becker, S. Iden, B. Wirth, P. Eysel, F. Koerber, E. Schoenau, S.K. Bohlander, B. Wollnik, C. Netzer, 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 (2012) 349–357.

[61] M. Doyard, S. Bacrot, C. Huber, M. Di Rocco, A. Goldenberg, M.S. Aglan, P. Brunelle, S. Temtamy, C. Michot, G.A. Otaify, C. Haudry, M. Castanet, J. Leroux, J.P. Bonnefont, A. Munnich, G. Baujat, P. Lapunzina, S. Monnot, V.L. Ruiz-Perez, V. Cormier-Daire, FAM46A mutations are responsible for autosomal recessive osteogenesis imperfecta, J. Med. Genet. 55 (2018) 278–284.