REVIEW

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Osteoporosis of genetic origin: a literature review

Artemis Doulgeraki

Department of Bone and Mineral Metabolism, Institute of Child Health, Athens, Greece

ABSTRACT

Numerous cases of genetic (primary) osteoporosis are reported in the literature, thanks to the in-depth investigation of suspicious scenarios, where a child or young adult presents with bone fragility. Thorough diagnostic work up is required in order to exclude more frequent, treatable, secondary causes of osteoporosis (e.g. leukaemia or Crohn's disease). When first line investigations exclude secondary osteoporosis and in the presence of specific clinical clues (e.g. blue sclerae, joint laxity) or of a suspicious family history of early onset osteoporosis, a genetic work up should be undertaken. There are many new genes implicated in the pathogenesis of primary osteoporosis, playing different roles in bone formation and/or resorption, depending on the metabolic bone path involved. The greater understanding of the complexity of bone metabolism opens new research roads for new, gene-specific treatments. Herein, the latest literature data on the osteoporosis of genetic origin are being presented. Emphasis is also given on the importance of lateral thinking, when it comes to children and young adults whose fracture history is remarkable and cannot be attributed solely to injury. Finally, the importance of not missing significant chronic disorders leading to osteoporosis is also highlighted.

KEYWORDS: osteoporosis, children, genes, metabolism, fractures

Introduction

Osteoporosis is the most frequent metabolic bone disorder, characterized by the presence of bone fragility, which predisposes to fractures, as a result of defective bone microarchitecture and reduced bone mass[1]. It is a multifactorial and complex disorder, affected by multiple factors which impair bone quality and quantity. Previously considered mostly a disease of the elderly, it is now increasingly diagnosed in younger populations, even in small children with chronic disorders that affect the skeleton or with intrinsic, heritable bone abnormalities.

The definition of osteoporosis varies, depending on the age group involved. In men>50 years old and post-menopausal women, where osteoporosis is more prevalent, according to the International Society of Clinical Densitometry (ISCD), a bone mineral density (BMD) T-score ≤ -2.5 , measured with dual X-ray absorptiometry (DXA) of the lumbar spine and/or hip, signifies osteoporosis[2]. In premen-

CORRESPONDING AUTHOR, GUARANTOR

Dr Artemis Doulgeraki, MD, PhD, MRCPCH, FRCPCH
email: doulgeraki@ich.gr, tel: +30 213 2037 360,
fax: +30 210 7700111

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 1.

Genes implicated in the pathogenesis of osteogenesis imperfecta.

Gene	Encoded protein	Type of inheritance
COL1A1	Collagen type I α1 chain	AD
COL1A2	Collagen type I α2 chain	AD
IFITM5	BRIL	AD
P3H1	Prolyl 3-hydroxylase 1	AR
CRTAP	Cartilage-associated protein	AR
PPIB	Peptidylprolyl isomerise B	AR
BMP1	Bone morphogenetic protein 1	AR
SERPINH1	Heat-shock protein 47	AR
SERPINF1	PEDF	AR
CREB3L1	OASIS	AR
SP7	Osterix	AR
TMEM38B	Transmembrane protein 38B	AR
WNT1	Wnt family member 1	AR
SPARC	Osteonectin	AR
TENT5/FAM36A	Terminal nucleotidyltransferase 5A	AR
MBTPS2	S2P	XLR

BRIL: Bone-restricted interferon-induced transmembrane protein-like protein, PEDF: Pigment epithelium-derived factor, OASIS: Old astrocyte specifically induced substance, S2P: membrane-bound transcription factor peptidase, site 2

opausal women and men<50 years old, the use of BMD Z-scores is preferred; values <-2 are considered as "low for age" [3]. Alternatively, according to the International Osteoporosis Foundation (IOF), it is possible to use T-score also for young adults; values <-2.5, in combination with history of chronic disease affecting the skeleton, are indicative of osteoporosis [4].

Regarding paediatric population, osteoporosis is rare but is now increasingly diagnosed in high risk patients; more and more cases are being discovered and treated. The growing skeleton is unique in that there is not only bone remodeling (continuous bone turnover cycle), but also bone modeling, i.e. accumulation of new bone, which gradually changes bone dimensions and enables growth. What is more important, is the fact that childhood is the "window of opportunity" for peak bone mass (PBM) achievement. Not surprisingly, it is estimated that a 10% increase in PBM may delay the onset of osteoporosis by thirteen years [5]. In other words, PBM achievement predicts bone health in adulthood [6].

However, children are not small adults, therefore the definition of osteoporosis in this age group is totally different. According to the paediatric ISCD guidelines [2], low DXA BMD Z-scores alone (<-2 in lumbar spine and/or total body less head, corrected for bone size, where appropriate) are not sufficient for diagnosis. A significant fracture history should also exist: either at least one non-traumatic vertebral fracture (regardless of BMD Z-score values) or at least three low-energy long bone fractures for those patients aged <19 years or at least two, if the patients are smaller (<10 years old). Admittedly, established osteoporosis is rare in children, but prompt diagnosis and treatment are crucial.

Depending on the underlying cause, osteoporosis is further classified into secondary (90% of cases), as a result of a chronic disease and /or its treatment (e.g. chronic use of systemic corticosteroids) and primary or genetic (10% of cases), attributed to a heritable bone disorder, thus occurring usually earlier, the so-called "early onset osteoporosis". When no identifiable cause is found after a comprehensive diagnostic work up, the term used is "idiopathic osteoporosis" and this is a diagnosis of exclusion, which is now

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

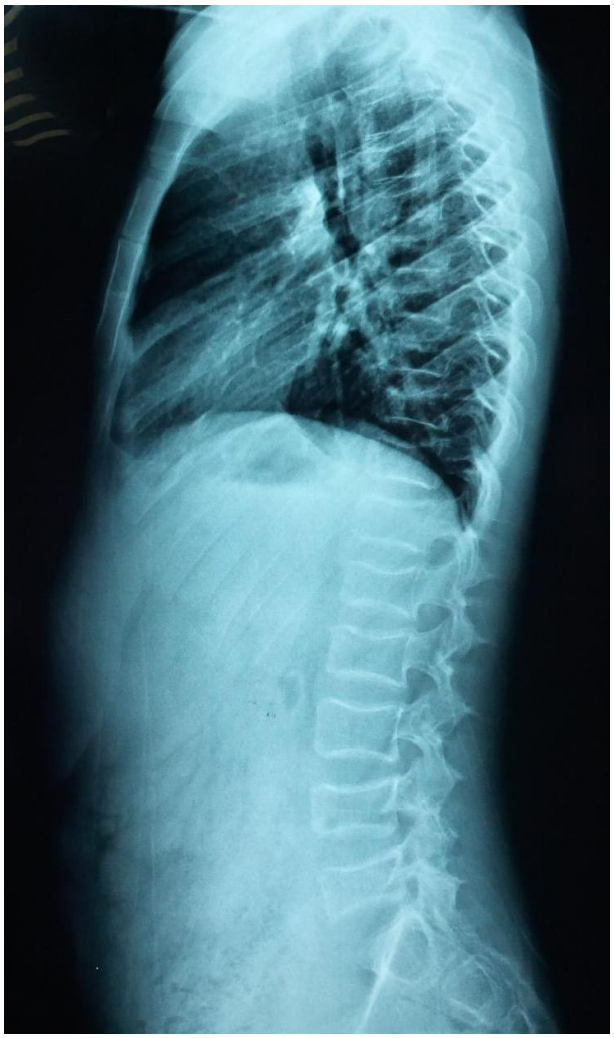

Fig. 1. *Multiple vertebral fractures of moderate severity in a 12-year-old boy with osteogenesis imperfecta (COL1A1 mutation) (Institute of Child Health archive)*

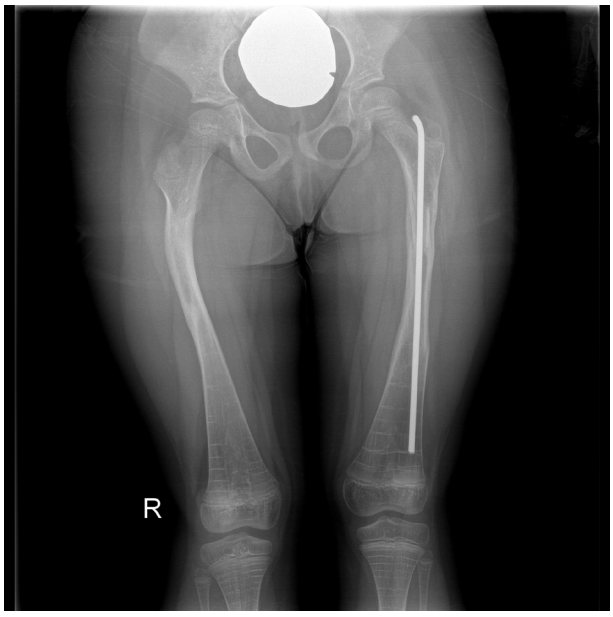

Fig.2. *Femoral deformities and rodding of left femur in a girl with osteogenesis imperfecta (COL1A2 mutation). Note the "zebra lines", due to treatment with zolendronic acid. (Institute of Child Health archive)*

less and less encountered, because of the discovery of new genes implicated in bone fragility [7].

This review will highlight the latest literature data on primary osteoporosis, which is genetic in origin and is suspected mostly in children and young adults. It is a group of heterogeneous inheritable disorders with different pathophysiology, depending on the gene involved. The intense research interest in these cases globally has enabled the scientific community to discover new metabolic bone pathways and diagnostic biomarkers and, most importantly, new treatments.

Types of primary osteoporosis and their pathophysiology

Genetic osteoporosis is attributed to monogenic disorders; however, with the advance in the diagnostic methodology, cases with a polygenic profile are also described.

Bone is a dynamic tissue; it undergoes considerable changes during growth. Even after growth plate fusion, bone remodeling continues for life and requires the complex coordination between the osteoblasts (bone formation), the osteoclasts (bone resorption) and the osteocytes. The differentiation and function of the aforementioned bone cells is regulated by specific signaling metabolic pathways. Moreover, the mineralization process is equally important for bone integrity and contributes to optimal bone quality.

Monogenic primary osteoporosis

The advent of extensive genetic testing not only of the index case but also of the whole family, has enabled the detection of > 35 monogenic disorders leading to early onset osteoporosis[8,9]. They show Mendelian inheritance and they are caused by mutations of genes which are very important in bone

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

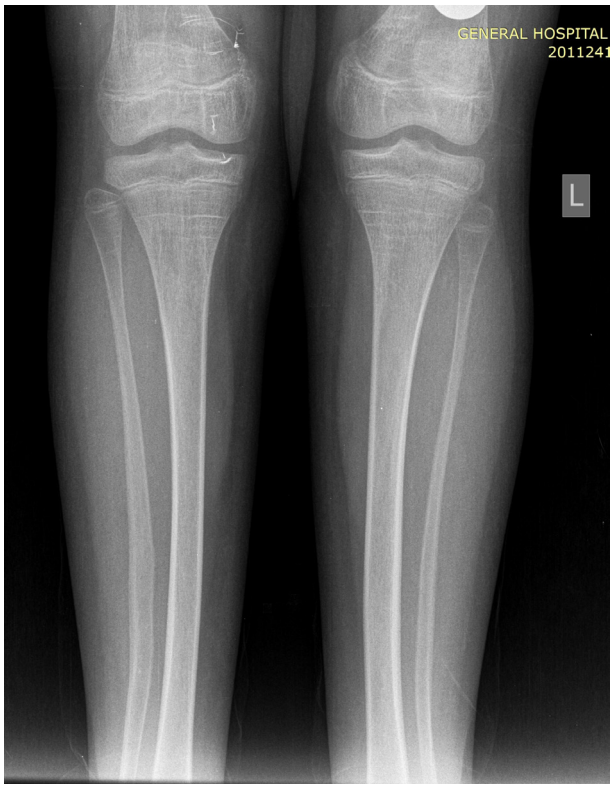

Fig.3. *Very slender and diffusely osteopenic tibiae and fibulae in a girl with osteogenesis imperfecta (COL1A1 mutation) (Institute of Child Health archive)*

homeostasis.

The most frequent entity of primary osteoporosis is osteogenesis imperfecta (OI) or brittle bone disease. It is an inherited connective tissue disorder, with prevalence of 1/10,000-1/20,000 births, caused mainly by mutations in COL1A1 or COL1A2 genes (85-90% of cases) [10]. These genes regulate the most abundant matrix protein, type I collagen [11], by encoding its two alpha chains. To date, eighteen other genes have been associated with the same phenotype and comprise the remaining 10-15% of cases. They are associated with the final stages of collagen modification or they play part in osteoblast differentiation or in the mineralization process. The list of OI genes is illustrated in table 1.

OI shows remarkable heterogeneity in terms of severity, even within the same family and this implies the existence of genetic modifiers affecting the spectrum of the phenotype. The impact of the mutation depends on the function of the affected gene and the type of pathogenic variant. OI patients show a ten-fold increase in the probability of fracture at a young age (0-19years), compared to the general population, according to Danish data [12]. Apart from the increased fracture rate (long bones and vertebral bodies, even in utero, in severe cases) (Fig.1, 2), these patients may also have bone deformities, severely osteopenic and slender bones (Fig.3), as well as short stature. OI is also characterized by its extraskeletal manifestations, such as deafness blue/grey sclerae, dentinogenesis imperfecta, joint laxity, basilar invagination, cardiac valve prolapse, easy bruisability and pulmonary hypoplasia in severe cases [13].

In terms of OI clinical types, the revised Sillence classification, which includes five different phenotypes, irrespective of the gene involved, is now used in clinical practice. Type I is the mildest form, type II is lethal, type III is the most severe form and type IV (no blue or grey sclerae) is of moderate severity. The new type V OI is distinct from the others in that there is calcification of the intraosseous membranes and hypertrophic callus post-fracture [14].

There are cases of genetic osteoporosis where there are no extraskeletal manifestations or severe bone deformities, despite a significant fracture history. These patients may be diagnosed later in adulthood, because their fractures are initially attributed to the active lifestyle of childhood, when in fact there are underlying mutations in specific genes, which play a pivotal role in bone metabolism. To date, the following genes have been described in more detail:

SGMS-2: This gene encodes Sphingomyelin Synthase-2, which is implicated in the synthesis of sphingomyelin. This phospholipid plays an important role in cholesterol metabolism, being a major lipid of the plasma membrane and thus important for cell signaling. Its exact mechanism of action with regards to bone turnover is still under investigation. Patients carrying mutations of this gene present with autosomal dominant osteoporosis, thin cortices of the long bone and calvarial doughnut lesions [15, 16]. Another potentially distinctive feature of this disorder is the presence of neurological symptoms as the main extraskeletal defect, particularly facial nerve palsy, which is usually transient [15].

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

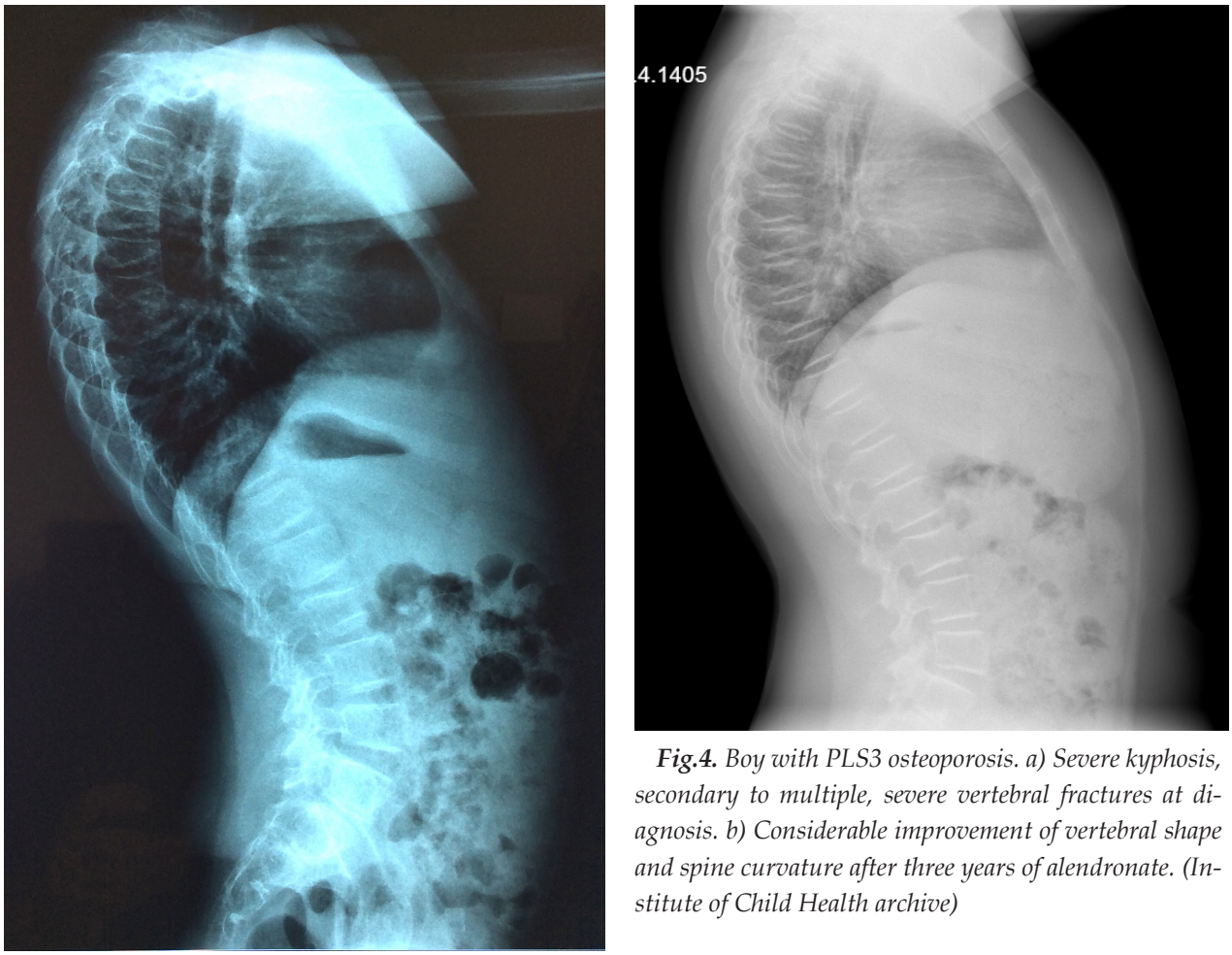

Fig.4. *Boy with PLS3 osteoporosis. a) Severe kyphosis, secondary to multiple, severe vertebral fractures at diagnosis. b) Considerable improvement of vertebral shape and spine curvature after three years of alendronate. (Institute of Child Health archive)*

PLS-3: Mutations of this gene cause X-linked osteoporosis, especially of the spine [17, 18]. As expected, male subjects show a more severe phenotype than their female counterparts, who can also present with fractures, usually at a later stage in life [19]. Plastin-3, the protein encoded by this gene, is implicated in the function of osteocytes, which serve as the mechanoreceptors of bone. This protein contributes to the integrity of the cytoskeleton, defining the shape of these bone cells [20].Dickkopf-1 (DKK-1), an inhibitor of the WNT signaling pathway, has been found increased in these patients and this contributes to their unfavourable bone profile [21].

WNT1: This gene is implicated in the WNT-β-catenin metabolic bone pathway, which controls mature osteoblast differentiation and bone development [22]. A gene dosing effect is apparently present. This is because the biallelic mutations of this gene lead to severe autosomal recessive OI, whose hallmark is the presence of ptosis [23], whereas its heterozygous mutations may cause autosomal dominant osteoporosis. There is low bone mass, long bone fractures and particularly slender fibulae during childhood [24] and vertebral fractures (with subsequent kyphosis) in adulthood [25].Surprisingly, a specific biomarker for this disorder is fibroblast growth factor-23 (FGF-23, both intact and C-terminal), whereas sclerostin and DKK-1, markers which are directly implicated in the WNT pathway, were not significantly different than controls in one study [26].

LRP5: LDL receptor-related 5 is a co-receptor for WNT ligands, therefore its mutations lead to abnormal bone metabolism and usually low bone formation markers [27]. Of interest, homozygous mutations cause osteoporosis-pseudoglioma syndrome, which is an important differential of OI, as

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

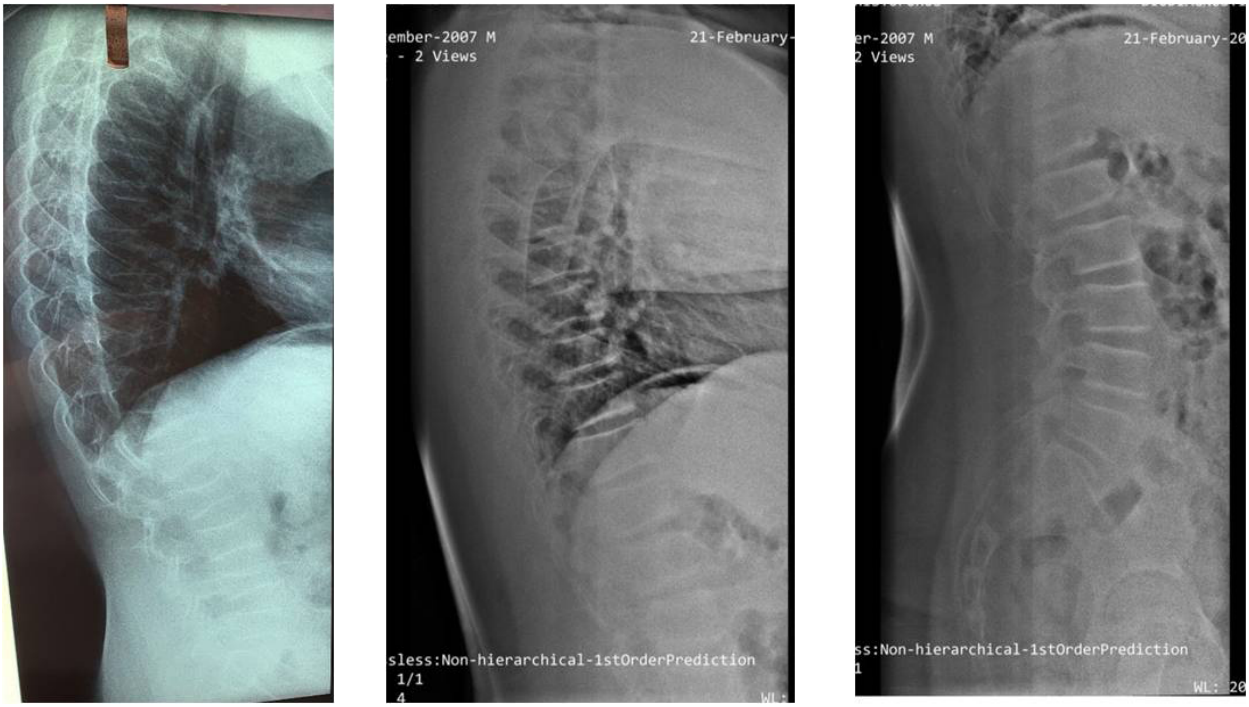

Fig. 5. *Boy with LRP5 osteoporosis. a) Kyphosis and severe, multiple vertebral fractures at diagnosis. b,c) Vertebral reshaping after three years on zolendronic acid. (Institute of Child Health archive)*

it combines early onset osteoporosis with blindness [28, 29]. On the other hand, heterozygous mutations cause osteoporosis with minimal or no eye involvement (Fig.5) [30].The presence of LRP5 variants is relatively common in cases with primary osteoporosis, estimated at 8.3%, according to a study of 372 patients [27]. These variants have also been associated with abnormal lipid profile and a tendency towards diabetes type II [31, 32].

NOTCH: Activating mutations of this gene enhance osteoclast maturation, through the RANK signaling mechanism, which in turn is affected by the NOTCH signaling pathway [33]. Hadju-Cheney syndrome results form autosomal dominant mutations of NOTCH2. Its main features are severe primary osteoporosis, combined with craniofacial dysmorphism and acroosteolysis [34]. Wormian bones may also be present. The key mechanism is the increased bone resorption, which is confirmed in specimens of bone biopsy [35].

TGF-β: Disorders TGF-β pathway lead to several skeletal diseases. This complex pathway is important for intracellular signal transmission, as it regulates cell activity in bone and cartilage. Depending on the mutations involved, the entities attributed to TGF-β disorders are Camurati-Engelmann disease, OI, Loeys-Dietz and Marfan syndromes [36-39].

For completeness, other monogenic diseases leading to early bone fragility are illustrated in table 2.

The polygenic aspect of primary osteoporosis

To assume that genetic osteoporosis is always monogenic is a rather simplistic approach and it does not account for the increased variability of phenotype amongst patients carrying the same disease variants. Thanks to genome-wide association studies, bone fragility is now considered multifactorial. In other words, genetic risk can be modified by the presence of common variants which explain the reduced bone mineral density [40, 41].

However, even in young patients who do not suffer from monogenic osteoporosis, their genetic profile maybe compatible with the presence of common fracture risk alleles [40]. In other words, it is possible that in some young patients their bone fragility is of polygenic rather than monogenic. This is a great diagnostic challenge; methods to quantify the polygenic contribution in cases of early-onset osteopo-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

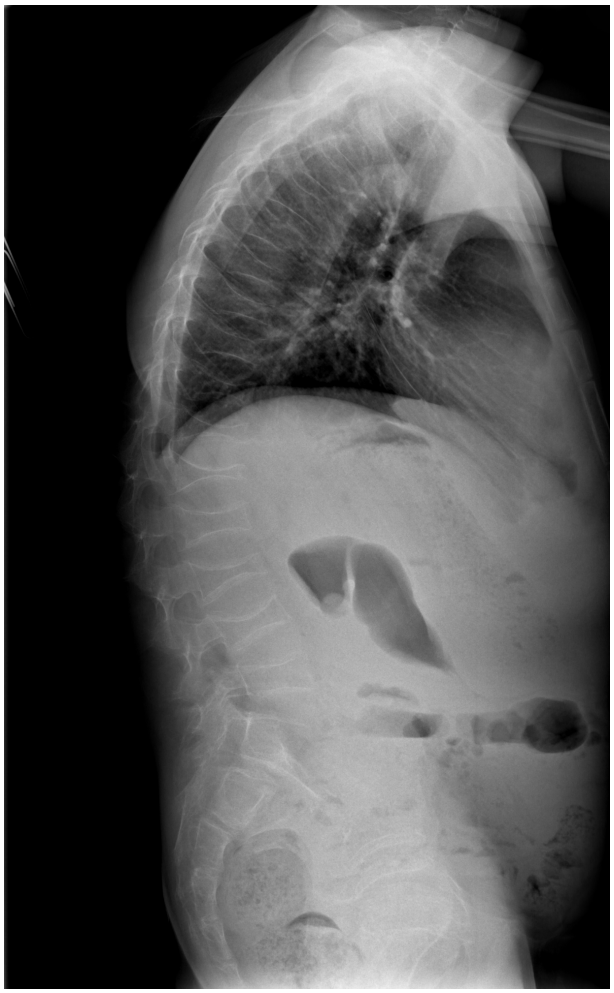

Fig.6. *Boy with severe osteoporosis (multiple, severe vertebral fractures), secondary to Crohn's disease. Of note, his first complaint was back pain. (Institute of Child Health archive)*

rosis are currently being explored. Epigenetics also contribute greatly to the understanding of osteoporosis occurrence. The term includes processes such as DNA methylation, non-coding RNAs (miRNAs) and histone changes. Collectively, they control gene expression without an effect on DNA sequences [42]. There is also the scenario of coexistence of two rare, different mutations in candidate genes for osteoporosis in the same patient; a case of a subject with both WNT1 and PLS3 pathologic variants has been reported [43].

When to suspect genetic osteoporosis

The earliest the primary osteoporosis is diagnosed, the better the outcome, especially in view of specific treatments available and also of the effect that such a diagnosis exerts on the patient and on the whole family. Given that this type of osteoporosis is considered "early onset", thus involving children and young adults, prompt intervention during the "window of skeletal growth" is of utmost importance. Referral should be made to a disciplinary team, led by a bone specialist, experienced in correctly diagnosing these rare disorders, carefully differentiate them from equally severe, secondary causes of osteoporosis (illustrated in Table 3) and aware of bone pathophysiology and growth potential.

A thorough history needs to be taken, starting from the prenatal period. Information of the presence of intrauterine fractures (reduced fetal movements), low bone mineralization and abnormal skeletal dimensions are clues to underlying, severe bone pathology. As a general rule, the smaller the age of the patient, the more likely the presence of genetic osteoporosis (after exclusion of non-accidental injury in non-verbal patients, i.e. infants and toddlers). Fracture history is obviously crucial and should be elucidated in detail (number of fractures, mechanism, location, treatment, review of all imaging studies available). The presence of vertebral fractures is also key to diagnosis; the patient is asked specifically for back pain. Lifestyle profile (exercise, diet) is explored, as well as past medical history for comorbidities and the use of medications known to affect the skeleton (e.g. corticosteroids). Growth parameters should be plotted on growth charts and pubertal status should be assessed. Lastly, family history is recorded meticulously, targeted not only on the presence of early osteoporosis in other members, but also on its complications, such as cardiac valve insufficiency, deafness, nephrocalcinosis and disorders of vision. Of note, the parents should be asked for their place of origin, in view of the fact that in closed, rural populations there might be consanguinity or particular gene mutations affecting the skeleton [44].

Special clues to the diagnosis of primary osteoporosis can be found during a head-to-toe clinical examination. Joint and skin laxity, grey or blue sclerae, tenderness on palpation of vertebrae, kyphosis

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 2.

Monogenic forms of osteoporosis

Syndrome	Gene	Encoded protein	Type of inheritance
Bruck 1	FKBP10	65kDa FK506-binding protein	AR
Bruck 2	PLOD2	Lysyl Hydrolase 2	AR
Hajdu-Cheney	NOTCH2	Notch receptor 2	AD
Ehlers-Danlos 1	PLOD1	Lysyl Hydrolase 1	AR
Ehlers-Danlos 2	FKBP14	FK506-binding protein 14	AR
Cole-Carpenter 1	P4HB	Prolyl 4-hydroxylase subunit β	AD
Cole-Carpenter 2	SEC24D	SEC24 homolog D	AR
Cutis laxa 2A	ATP6VOA2	ATPaseH+ transporting VO subunit	AR
Cutis laxa 2B	PYCR1	Pyrroline-5-carboxylase reductase 1	AR
Geroderma osteodysplasticum	GORAB	Golgin, RAB6 interacting	AR
Familial expansile osteolysis	TNFRSF11A	TNF receptor superfamily member 11A	AD
Gnathodiaphyseal dysplasia	ANO5	Anoctamin 5	AD

and skeletal malformations raise suspicion towards inheritable causes of osteoporosis rather than acquired. A very helpful finding in some cases is the presence of yellow-brown or grey, transparent teeth, suggestive of dentinogenesis imperfecta, therefore dental inspection should always be part of the clinical examination.

However, the differential diagnosis between the monogenic forms of primary osteoporosis can be challenging, as the clinical signs show significant overlap; nevertheless, as data are accumulating, it is possible to look for specific features. For instance, in PLS3 patients there seems to be a tendency towards severe vertebral fractures and kyphosis at a young age, as a hallmark [45] (Fig.4), whereas this type of fractures appears only in adulthood in the WNT1 osteoporosis [19, 46]. Another key differential is the presence of extraskeletal manifestations. For example, WNT1 mutations also affect the central nervous system, therefore neurological abnormalities, such as epilepsy, cerebellar hypoplasia and global developmental delay raise suspicion towards this direction [47].The same is true for SGMS2 cases, where nerve palsies are occasionally observed, e.g. transient facial palsy, along with global developmental delay [45].

Diagnostic work up

As mentioned in the introduction, there are specific diagnostic criteria for osteoporosis in children and young adults. When these criteria are met, the next important step is to exclude causes of secondary osteoporosis and child abuse in infants and toddlers with unexplained fractures. Diseases with special treatment and potentially life-threatening are not to be missed. For example, the first presentation of leukaemia and Crohn's disease can be a vertebral fracture (Fig. 6).On the other hand, there are high profile cases in courts where parents of babies with OI have wrongly been accused of non-accidental-injury and vice versa, i.e. small children being investigated for an underlying genetic disorders, when in fact they have been victims of abuse [48,49].

Therefore, after obtaining a comprehensive medical history and performing a thorough clinical examination, a laboratory evaluation of blood and urine is necessary, targeting known causes of secondary osteoporosis. As a general rule, basic bone profile is always performed (including 24h urine collection for calcium or spot sample for uCa/uCreat of a fasting, 2nd morning void), along with complete blood count, erythrocyte sedimentation rate, C-reactive protein, thyroid function tests and testosterone in boys. Thereafter, depending on the clinical scenario, other hormonal investigations can be undertaken, along with tryptase, ferritin and celiac screening, as

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 3.

Secondary causes of osteoporosis that need to be excluded in every patient with early bone fragility

Disease groups	Others
Endocrine Growth hormone deficiency or excess Hypogonadism Hyperthyroidism Hyperparathyroidism Diabetes 1 and 2 Hypopituitarism Cushing's disease/syndrome	Cerebral palsy HIV Chronic immobility Duchenne's muscular dystrophy Bone marrow transplantation Solid organ transplantation Renal failure Mastocytosis Pregnancy/Breastfeeding
Chronic inflammation Inflammatory bowel disease Systemic lupus erythematosus Rheumatoid arthritis Sarcoidosis	
Haematology Leukaemia Lymphoma Thalassaemia major Haemophilia Multiple myeloma Haemochromatosis	Medications Corticosteroids Chemotherapy Anticonvulsants HAART Proton pump inhibitors Heparin Aromatase inhibitors LHRH agonists Tamoxifen Thiazolidinediones
Malnutrition/malabsorption Cystic fibrosis Chronic liver disease Rickets Coeliac disease Short gut syndrome Anorexia nervosa	
Inborn errors of metabolism Gaucher's disease Hypophosphatasia Glycogen storage disease Homocystinuria Mucopolysaccharidoses Pompe disease	

HIV: Human Immunodeficiency Virus, HAART: Highly Active Anti Retroviral Treatment, LHRH: luteinizing hormone-releasing hormone

is shown in table 4. There is no paediatric consensus on the diagnostic use of bone turnover markers at a young age; however, they are valuable tools for monitoring of anti-osteoporosis treatment.

Imaging studies necessary for diagnosis include dual-energy X-ray absorptiometry (DXA), review of all X-rays available to check for fractures and deformities, as well as lateral X-rays of the spine, to look for vertebral fractures, especially if there is low BMD, kyphosis, height loss or tenderness on palpation of the spine. In cases where non-accidental injury is suspected, a skeletal survey of the whole skeleton is performed (baseline and follow up), in order to detect new and old fractures and pick up specific signs suggestive of an intrinsic bone defect (e.g. diffuse osteopenia, rachitic changes, slender bones, wormian bones), thus contributing to the differential diagnosis [50].

Ideally, a transiliac bone biopsy should be obtained in order to study the pathophysiology behind a particular phenotype, i.e. to differentiate between high and low bone turnover states, using histomor-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 4.

Diagnostic laboratory work up to exclude secondary osteoporosis in patients with early bone fragility	
First line, indicated in all patients	
Test	To exclude
Basic bone profile*	Disorders of calcium and phosphate metabolism, hypercalciuria, HPP
CBC	Haematological disorders
ESR, CRP	Inflammatory conditions
TFTs	Hyperthyroidism
Testosterone	Male hypogonadism
Glucose, HbA1C	Diabetes mellitus
Bone turnover (e.g. PINP, CTx)	Baseline before bone-active treatment
Second line, depending on history and examination	
Tryptase	Mastocytosis
Ferritin	Haemochromatosis
Sex hormones	Delayed/absent puberty
IGF-1	Acromegaly or GH deficiency
Urinary cortisol	Cushing's syndrome
Coeliac antibodies	Coeliac disease
Fat-soluble vitamins	Malabsorption

**: Basic bone profile includes (fasted serum and fasted 2nd morning void): calcium, phosphate, magnesium, alkaline phosphatase, creatinine, albumin, liver function tests, 25(OH)D, parathormone and urinary calcium/urinary creatinine, urinary phosphate/urinary creatinine*

CBC: complete blood count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TFTs: thyroid function tests (free T4 and TSH), IGF-1: insulin-like growth factor 1, PINP: procollagen type I N-propeptide, CTx:carboxy-terminal cross-linking telopeptide of type I collagen, HPP: hypophosphatasia

phometry techniques. New, promising treatments target different bone metabolic paths, so this information could facilitate the best possible selection of treatment for each individual case. However, this diagnostic approach is too interventional, requires expertise and special equipment, therefore it is not at all popular in routine clinical practice.

When secondary causes have been excluded, appropriate genetic tests are the last resort, in an effort to reveal the underlying cause of osteoporosis. Suspicious family history and clinical signs pointing to a genetic cause show great variability, therefore it is necessary to confirm this suspicion with genetic work up. In addition, identifying the disease-causing mutation enables appropriate genetic counseling (and family planning, as a result), enables prognostication and allows treatment plans, tailored to the patient's needs. Taking into account that COL1A1 and COL1A2 mutations comprise 85-90% of the genetic cases, these two genes should be checked for in every analysis, as a minimum. With the advent of new, cost-effective diagnostic technology, it is now possible to screen for other monogenic forms of primary osteoporosis, by studying appropriate gene panels for bone fragility using next generation sequencing (NGS). These commercially available panels should be constantly updated, to include new candidate genes for osteoporosis. This pitfall may be avoided by using whole exome sequencing (WES).

As more and more genes are being discovered as causative factors of early osteoporosis, it is very important to have access to data which can be reanalyzed in due course. Performance of WES or whole genome sequencing (WGS) is now possible and contributes to the constantly accumulating knowledge on these rare disorders. By using these methods, the sequencing data are filtered appropriately to detect potentially disease-causing variants. It is hoped that

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

with time, these methods will be more and more accessible. In fact, with the contribution of bioinformatics, WGS may become standard practice in the future, because it may detect coding or non-coding or structural variants [51]. Until then, guidelines for genetic work up will vary between different centers and different countries, depending on the case load, local resources and available expertise. It should be noted that no genetic test is a substitute for detailed history and clinical assessment; in other words, a meticulous description of the phenotype and the family tree are prerequisites for the interpretation of genetic results, as they enable their filtering and interpretation. This is particularly true when a "variant of unknown significance" (VUS) is detected.In this scenario, the study of family trios can be proved very useful. According to this approach, the parents of the index case are also screened, to check the inheritance pattern of a specific variant.

Therapeutic approach of genetic osteoporosis

The rarity of the primary osteoporosis cases, combined with the usually small age of the patients leads to relatively few data from clinical studies, with regards to bone-active medications. Most research works focus on OI, whereas the other monogenic forms have not been extensively studied.In principle, a skilled multidisciplinary team, with expertise in bone disease in the young subjects, undertakes the challenging task of treating the patient using a personalized approach.

Lifestyle advice is always given. All patients with primary osteoporosis need to ensure adequate dietary intake of calcium and vitamin D and take supplements, where appropriate. In fact, small studies have shown a beneficial effect of calcium and vitamin D co-administration on bone mineral density [52, 53]. Exercise is equally important and plays a protective role for bone health [54]. In adolescents and young adults, advice on avoidance of smoking and alcohol use is offered, as these habits can have deleterious effects on the skeleton. Moreover, if there is a history of a comorbidity that affects bone health, it should also be addressed efficiently [7], e.g. a patient with OI and uncontrollable asthma, requiring frequent administration of oral steroids.

Supportive treatment is also crucial; it involves proper fracture management, aiming at improving mobility, as well as physiotherapy, occupational therapy, orthopaedic procedures to improve skeletal malformations (e.g. rodding, Fig.2) and mobility aids. Depending on the severity of osteoporosis, first line, bone active medications, with proved efficacy in improving BMD and quality of life (QOL) are bisphosphonates, which are used "off label" during childhood, in most countries. Thanks to the discovery of the aforementioned rare, monogenic forms of primary osteoporosis, new bone metabolic pathways have been investigated, allowing research on new drugs, with a view to a more individual approach towards the patient, for the best possible therapeutic results.

Bisphosphonates (BPs) are the first line treatment in primary osteoporosis. Most literature data describe their effects in OI patients and the majority focus in intravenous treatment with either pamidronate or zolendronic acid. BPs show an anti-resorptive effect on bone, i.e. they act on the osteoclasts, by binding to hydroxyapatite and inducing osteoclast apoptosis. They don't contribute to the accumulation of new bone; rather, they prevent bone loss, they promote vertebral reshaping (Fig.4, 5) and the net result is an increase in BMD. Their effects when given either orally or intravenously on fractures is less clear; a recent Cochrane review reports that no firm conclusion can be drawn regarding bisphosphonate use and fracture incidence [55].

Nevertheless, they are considered first line treatment of all forms of primary osteoporosis for the time being. On the other hand, there are major concerns surrounding their use. For example, BPs are retained in bone for many years, therefore it is important to discuss a future pregnancy with a female patient of reproductive age. Despite the fact that a small case study did not report major events during pregnancy, such as teratogenesis, neonatal complications cannot be totally excluded [56], therefore it is advisable to avoid BPs for at least a year before pregnancy [57]. Another vivid discussion in on the use of BPs and the risk of osteonecrosis of the jaw and also of atypical femoral fractures [58].

Another therapeutic agent which acts on osteo-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

clasts is denosumab, a monoclonal antibody which acts as a RANKL inhibitor; it increases BMD and has been approved for post-menopausal osteoporosis. As RANKL is involved in the osteoclast maturation, its inhibition by this monoclonal antibody blocks this process. Given that most primary osteoporosis cases are diagnosed in childhood, its use for this indication in this particular age group is thus far limited and research is ongoing. Important points for clarification are the rebound of increased bone turnover (risk of severe hypercalcaemia in young patients [59]), the occurrence of vertebral fractures after cessation of treatment, as well as the duration of the therapeutic effect [60]. In other words, more paediatric studies are needed for its use in genetic osteoporosis. Regarding pregnancy, it can be hypothesized that no major effects will be observed after stopping denosumab. This is because the drug is not retained in the skeleton.

There are also anabolic treatments available and are also being investigated in primary osteoporosis. Currently there is no formal consensus on their use in such cases, however they are mentioned here for completeness, given that the discovery of new genes implicated in osteoporosis has led to the study of new metabolic pathways, regulating bone formation rather than resorption.

Teriparatide (human PTH analogue) has been in use for many years; due to a black-box warning for risk of osteosarcoma in young rats, its use in paediatric patients is still contraindicated. There are numerous OI cases of young adults [58], where teripatide has been prescribed. It activates osteoblasts, therefore contributes to increased bone formation. The TOPAZ study looks into the effect of coadministration of teriparatide and zolendronic acid (or zolendronate) in adults with OI [61].

Growth hormone (GH) also shows an anabolic effect, as it stimulates bone growth; however, it is helpful when GH deficiency coexists and not in the OI scenario, when usually short stature is an intrinsic defect, correlated with disease severity. Nevertheless, it has been given off-label in cases of OI type I and IV [55].

Relatively new drug discoveries in the field of osteoporosis, with trials under way on genetic osteoporosis, are targeted towards the WNT metabolic pathway (anti-sclerostin antibodies, i.e. setrusumab and romososumab) and the TGF-β pathway (fresolimumab and losartan).

Sclerostin is a potent WNT inhibitor which is produced mainly by osteocytes and contributes to the control of bone formation [62]. The sclerostin antibody romosozumab was approved for osteoporosis treatment in 2019 and there are trials of this drug on OI patients [63]. Caution should be exerted with regards to its cardiovascular safety profile, given the contribution of WNT pathway in vascular calcifications and atherosclerosis [64]. Setrusumab is another sclerostin inhibitor and is also being investigated in adults with moderate OI [65].

Fresolimumab is related to the TGF-β pathway, which influences both bone formation (reduced osteoblast function) and-mostly-bone resorption, through stimulation of osteoclastogenesis [66]. It is a monoclonal antibody which blocks TGF-β. Animal studies have shown its efficacy in increasing bone mass and improving bone quality [67]. Currently it is being tried in adult patients with moderate or severe OI [68]. Losartan, an angiotensin II type 1 receptor blocker, may also inhibit TGF-β signaling [69]. This agent has been tried in Camurati-Engelmann syndrome [70].

Future developments in primary osteoporosis

As the effect of epigenetics on osteoporosis is more and more highlighted in the literature, numerous efforts are made towards identifying more specific and sensitive biomarkers for fracture occurrence. Non-coding RNAs, such as micro-RNAs (miRNAs) act as epigenetic regulators involved in the control of gene expression, affecting bone metabolism (both formation and resorption), amongst other biological processes [71].For diagnosis and treatment monitoring, the study of miRNAs is expected to modify our approach to osteoporosis. They can be easily measured in many different biological fluids (e.g. saliva [72] or urine [73] and reflect lifestyle and general health status for each individual, in relation to the osteoporosis risk.

Revolutionary treatments which are very hopeful and expected to change the therapeutic landscape

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

of primary osteoporosis, are stem cells administration and treatments aiming at correcting the gene involved. Back in 2005, adult mesenchymal stem cells (MSCs) were given to six children with severe OI and the results were encouraging, in terms of fracture rate and growth [74]. As a next step, an ambitious, two-armed study is under way (BOOSTB4), where fetal MSCs are administered as antenatal treatment in OI cases, i.e. in utero (1st arm, MSCs given during the 2nd and 3rd trimester) or postnatally (2nd arm, MSCs given after birth). The follow up period will last for ten years [75].Although the MSCs seem promising, they are not curative, as the patient will end up having a mixed population of bone cells, i.e. normal and abnormal. There is also the theoretical risk of the MSCs evolving into cancer cells. The research on these matters is in progress.

The efforts for a curative solution in the field of primary osteoporosis are ongoing, with the exploration of gene and cellular therapy approaches. Sophisticated, new technologies targeting the mutated gene are being developed, such as prime editing, zinc finger nuclease, TALEN and CRISPR-CAS [76]. Antisense oligodeoxyribonucleotides to silence the dominant allele in OI are tested on an experimental level [77].A detailed description of these methods is beyond the scope of this review.

Conclusions

The field of genetic osteoporosis is constantly expanding. Exciting developments are awaited, both diagnostic and therapeutic, as new metabolic bone paths are revealed. In all rare diseases, increased awareness shortens the patient's diagnostic journey and leads to prompt interventions, with the ultimate goal of improving quality of life. This is especially important, when it comes to children and young adults, i.e. the usual age group with primary osteoporosis.

Lateral thinking is crucial in the clinical scenario of a young patient with history of recurrent fractures, especially when they are low energy fractures of if they involve the vertebrae. Careful physical examination of all systems for possible clues of primary osteoporosis and detailed history, with emphasis on family tree may be revealing. It is equally important to exclude treatable, secondary causes of osteoporosis at the same time and non-accidental injury in infants and toddlers. With the advent of sophisticated technology in genetics and the hope that this will become more and more cost effective and accessible in medical centers worldwide, case numbers will probably rise and a greater number of patients will benefit from new treatments. A

Conflict of interest: None declared.

Acknowledgements: The author wishes to thank the personnel of the Department of Bone and Mineral Metabolism at the Institute of Child Health for their dedication to the wellbeing of our young patients and their families (Dr Athanasopoulou, Dr Polyzois and Mr Psimitis).

REFERENCES

1. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors International Osteoporosis Foundation. Osteoporos Int 2000; 11:192–202
2. Lewiecki EM, Gordon CM, Baim S et al. International society for clinical densitometry 2007 adult and pediatric official positions. Bone 2008; 43(6):1115–1121.
3. Makras P., Anastasilakis AD, Antypas G et al. The 2018 Guidelines for the diagnosis and treatment of osteoporosis in Greece. Arch Osteopor 2019;14:39
4. Ferrari S, Bianchi ML, Eisman JA et al.IOF Committee of Scientific Advisors Working Group on Osteoporosis Pathophysiology. Osteoporosis in young adults: pathophysiology, diagnosis, and management. Osteoporos Int

2012; 23(12):2735–48.

5. Hernandez CJ, Beaupre GS, Carter DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. Osteoporos Int. 2003;14(10):843–7.
6. Kralick AE, Zemel BS. Evolutionary perspectives on the developing skeleton and implications for lifelong health. Front Endocrinol (Lausanne). 2020; 11:99
7. Mäkitie O, Zillikens MC. Early-onset osteoporosis. Calc Tissue Int 2022; 110:546–561
8. Mortier GR, Cohn DH, Cormier-Daire V et al. Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet A 2019; 179(12): 2393–419
9. van Dijk FS, Semler O, Etich J et al. Interaction between KDELR2 and HSP47 as a key determinant in osteogenesis imperfecta caused by bi-allelic variants in KDELR2. Am J Hum Genet 2020; 107(5):989-999
10. Marini JC, Forlino A, Bachinger HP et al. Osteogenesis imperfecta. Nature Rev Dis Primers 2017; 3: 17052
11. Forlino A, Marini JC. Osteogenesis imperfecta. Lancet 2016; 387(10028):1657–71
12. Folkestad L, Hald JD, Ersbøll AK et al. Fracture rates and fracture sites in patients with osteogenesis imperfecta: a nationwide register-based cohort study. J Bone Miner Res 2017; 32(1):125–34
13. El-Gazzar A, Högler W. Mechanisms of Bone Fragility: From Osteogenesis Imperfecta to Secondary Osteoporosis. Int J Mol Sci 2021; 22: 625
14. Warman, M.L, Cormier-Daire, V, Hall, C et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A 2011; 155A: 943–968.
15. Roschger P, Jain A, Kol M et al. Osteoporosis and skeletal dysplasia caused by pathogenic variants in SGMS2. JCI Insight 2019; 4(7):e126180
16. Robinson ME, Bardai G, Veilleux LN et al. Musculoskeletal phenotype in two unrelated individuals with a recurrent nonsense variant in SGMS2. Bone 2020; 134:115261
17. Van Dijk FS, Zillikens MC, Micha D et al. PLS3 mutations in X-linked osteoporosis with fractures. N Engl J Med 2013; 369(16):1529–36
18. Laine CM, Wessman M, Toiviainen-Salo S et al. A novel splice mutation in PLS3 causes X-linked early onset low-turnover osteoporosis. J Bone Miner Res 2015;30(3):510–8
19. Makitie RE, Niinimaki T, Suo-Palosaari M et al.PLS3 mutations cause severe age and sex-related spinal pathology. Front Endocrinol (Lausanne) 2020; 23(11):393
20. Tanaka-Kamioka K, Kamioka H, Ris H et al. Osteocyte shape is dependent on actin filaments and osteocyte processes are unique actin-rich projections. J Bone Miner Res 1998; 13(10):1555–1568.
21. Makitie RE, Kampe A, Costantini A et al. Biomarkers in WNT1 and PLS3 osteoporosis: altered concentrations of DKK1 and FGF23. J Bone Miner Res 2020;35: 901–12
22. Westendorf JJ, Kahler RA, Schroeder TM. Wnt signaling in osteoblasts and bone diseases. Gene 2004; 341:19–39
23. Nampoothiri S, Guillemyn B, Elcioglu N et al. Ptosis as a unique hallmark for autosomal recessive WNT1-associated osteogenesis imperfecta. Am J Med Genet A 2019; 179(6):908–914.
24. Makitie RE, Haanpaa M, Valta H et al. Skeletal characteristics of WNT1 osteoporosis in children and young adults. J Bone Miner Res 2016; 31(9):1734–1742
25. Laine CM, Joeng KS, Campeau PM et al. WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta. N Engl J Med 2013;368(19):1809–16
26. Makitie RE, Kampe A, Costantini A et al. Biomarkers in WNT1 and PLS3 osteoporosis:altered concentrations of DKK1 and FGF23. J Bone Miner Res 2020; 35(5):901–912.
27. Sturznickel J, Rolvien T, Delsmann A et al. Clinical phenotype and relevance of LRP5 and LRP6 variants in patients with early-onset osteoporosis (EOOP). J Bone Miner Res 2021; 36(2):271–282
28. Hartikka H, Makitie O, Mannikko M et al. Heterozygous mutations in the LDL receptor related protein 5 (LRP5) gene are associated with primary osteoporosis in children. J Bone Miner Res 2005; 20 (5):783–9
29. Gong Y, Slee RB, Fukai N et al. Osteoporosis-Pseudoglioma Syndrome Collaborative Group. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. Cell 2001; 107(4):513–23
30. Campos-Obando N, Oei L, Hoefsloot LH et al. Osteoporotic vertebral fractures during pregnancy: be aware of a potential underlying genetic cause. J Clin Endocrinol Metab 2014; 99(4):1107–1111.
31. Saarinen A, Saukkonen T, Kivela Tet al. Low density lipoprotein receptor-related protein 5 (LRP5) mutations and osteoporosis, impaired glucose metabolism and

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

hypercholesterolaemia. Clin Endocrinol (Oxf) 2010; 72(4):481–488

32. Foer D, Zhu M, Cardone RL et al. Impact of gain-of-function mutations in the low-density lipoprotein receptor-related protein 5 (LRP5) on glucose and lipid homeostasis. Osteoporos Int 2017; 28(6):2011–2017
33. Hilton MJ, Tu X, Wu X et al. Notch signaling maintains bone marrow mesenchymal progenitors by suppressing osteoblast differentiation. Nat Med 2008; 14: 306–314
34. Narumi Y, Min BJ, Shimizu K et al. Clinical consequences in truncating mutations in exon 34 of NOTCH2: Report of six patients with Hajdu-Cheney syndrome and a patient with serpentine fibula polycystic kidney syndrome. Am J Med Genet A 2013; 161A: 518–526
35. Sakka S, Gafni R.I, Davies J.H et al. Bone Structural Characteristics and Response to Bisphosphonate Treatment in Children With Hajdu-Cheney Syndrome. J Clin Endocrinol Metab 2017; 102: 4163–4172
36. Van Hul W, Boudin E, Vanhoenacker FM et al. Camurati-Engelmann Disease. Calcif Tissue Int 2019; 104: 554–560
37. Verstraeten A, Alaerts M, Van Laer L et al. Marfan Syndrome and Related Disorders: 25 Years of Gene Discovery. Hum Mutat 2016; 37: 524–531
38. Tan EW, Offoha RU, Oswald GL et al. Increased fracture risk and low bone mineral density in patients with Loeys-Dietz syndrome. Am J Med Genet A 2013; 161A:1910–1914.
39. Grafe I, Yang T, Alexander S et al. Excessive transforming growth factor-beta signaling is a common mechanism in osteogenesis imperfecta. Nat Med 2014; 20: 670–675
40. Manousaki D, Kampe A, Forgetta V et al. Increased burden of common risk alleles in children with a significant fracture history. J Bone Miner Res 2020; 35(5):875–882
41. Fahed AC, Wang M, Homburger JR et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nat Commun 2020; 11(1):3635
42. Kyoung-Tae K , Young-Seok L, Inbo H. The Role of Epigenomics in Osteoporosis and Osteoporotic Vertebral Fracture. Int J Mol Sci 2020; 21: 9455
43. Rocha-Braz MGM, Franca MM, Fernandes AM et al. Comprehensive genetic analysis of 128 candidate genes in a cohort with idiopathic,severe, or familial osteoporosis. J Endocr Soc 2020; 4(12):148
44. Ciancia S , van Rijn RR, Högler W et al. Osteoporosis in children and adolescents: when to suspect and how to diagnose it. Eur J Ped 2022; 181:2549–2561
45. Costantini A, Mäkitie RE, Hartmann MA et al. Early-Onset Osteoporosis: Rare Monogenic Forms Elucidate the Complexity of Disease Pathogenesis Beyond Type I Collagen. JBMR 2022; 37(9):1623–1641.
46. Makitie RE, Niinimaki T, Nieminen MT et al. Impaired WNT signaling and the spine-heterozygous WNT1 mutation causes severe age-related spinal pathology. Bone 2017;101:3-9.
47. Faqeih E, Shaheen R, Alkuraya FS. WNT1 mutation with recessive osteogenesis imperfecta and profound neurological phenotype. J Med Genet 2013; 50(7):491-492
48. Pomeranz ES. Child Abuse and Conditions That Mimic It. Pediatr Clin North Am 2018; 65(6):1135-1150
49. Pandya NK, Baldwin K, Kamath AF et al. Unexplained fractures: child abuse or bone disease? A systematic review. Clin Orthop Relat Res 2011;469(3):805-12
50. van Rijn RR, Sieswerda-Hoogendoorn T. Educational paper: imaging child abuse: the bare bones. Eur J Pediatr 2012; 171(2):215-24
51. Xuan J, Yu Y, Qing T et al.Next-generation sequencing in the clinic: promises and challenges. Cancer Lett 2013;340(2):284-295
52. Peris P, Monegal A, Martinez MA et al. Bone mineral density evolution in young premenopausal women with idiopathic osteoporosis. Clin Rheumatol 2007; 26(6):958–961
53. Islam MZ, Shamim AA, Viljakainen HT et al. Effect of vitamin D, calcium and multiple micronutrient supplementation on vitamin D and bone status in Bangladeshi premenopausal garment factory workers with hypovitaminosis D: a double-blinded, randomised, placebo-controlled 1-year intervention. Br J Nutr 2010; 104(2):241–247
54. Mayranpaa MK, Viljakainen HT, Toiviainen-Salo S et al. Impaired bone health and asymptomatic vertebral compressions in fracture-prone children: a case-control study. J Bone Miner Res 2012; 27(6):1413–1424
55. Kobayashi T, Nakamura Y, Suzuki T et al. Efficacy and Safety of Denosumab Therapy for Osteogenesis Imperfecta Patients with Osteoporosis—Case Series. J Clin Med 2018;7(12):479
56. Sokal A, Elefant E, Leturcq T et al. Pregnancy and new-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

born outcomes after exposure to bisphosphonates: a case control study. Osteoporos Int 2019; 30(1):221–229
57. Langdahl BL. Osteoporosis in premenopausal women. Curr Opin Rheumatol 2017; 29(4):410–415
58. Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. Orphanet J Rare Dis 2019; 14:300
59. Uday S, Gaston C.L, Rogers L et al. Osteonecrosis of the Jaw and Rebound Hypercalcemia in Young People Treated With Denosumab for Giant Cell Tumor of Bone. J Clin Endocrinol Metab 2018; 103: 596–603
60. Tsourdi E, Zillikens MC, Meier C et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. J Clin Endocrinol Metab 2020;26:756
61. Raulston S.Treatment of OI with PTH and Zoledronic acid 2018. https://ukctg.nihr.ac.uk/trials,trial number ISRCTN15313991
62. Van Bezooijen R.L, ten Dijke P., Papapoulos, S.E. et al. SOST/sclerostin, an osteocyte-derived negative regulator of bone formation. Cytokine Growth Factor Rev 2005; 16: 319–327
63. Tauer J.T, Robinson M.E, Rauch F. Osteogenesis Imperfecta: New Perspectives From Clinical and Translational Research. JBMR Plus 2019; 3: e10174
64. Gaudio A, Fiore V, Rapisarda R et al. Sclerostin is a possible candidate marker of arterial stiffness: Results from a cohort study in Catania. Mol Med Rep 2017; 15: 3420–3424.
65. Glorieux FH, Devogelaer JP, Durigova M et al. BPS804 anti-sclerostin antibody in adults with moderate osteogenesis imperfecta: results of a randomized phase 2a trial. J Bone Miner Res 2017; 32(7):1496–504
66. Wu M, Chen G, Li YP. TGF-β and BMP signaling in osteoblast, skeletal development, and bone formation, homeostasis and disease. Bone Res 2016;4:16009
67. Grafe I, Yang T, Alexander S et al. Excessive transforming growth factor-β signaling is a common mechanism in osteogenesis imperfecta. Nat Med 2014;20(6):670
68. Multicenter study to evaluate safety of fresolimumab treatment in adults with moderate to severe OI 2019 https://www. rarediseasesnetwork.org/cms/bbd/studies/7706
69. Mo C, Ke, J, Zhao D et al. Role of the renin-angiotensin-aldosterone system in bone metabolism. J Bone Miner Metab 2020; 38: 772–779
70. Ayyavoo A, Derraik JG, Cutfield WS et al. Elimination of pain and improvement of exercise capacity in Camurati-Engelmann disease with losartan. J Clin Endocrinol Metab 2014; 99: 3978–3982.
71. Yang Y, Yujiao W, Fang W et al. The roles of miRNA, lncRNA and circRNA in the development of osteoporosis. Biol Res 2020; 53:40
72. Gallo A; Tandon M, Alevizos I et al. The majority of microRNAs detectable in serum and saliva is concentrated in exosomes. PLoS ONE 2012; 7: e30679
73. Zhou Q, Li M, Wang X et al. X. Immune-related MicroRNAs are Abundant in Breast Milk Exosomes. Int J Biol Sci 2011; 8: 118–123
74. Le Blanc K, Gotherstrom C, Ringden O, et al. Fetal mesenchymal stem-cell engraftment in bone after in utero-transplantation in a patient with severe osteogenesis imperfecta. Transplantation 2005;79(11):1607–14
75. Crouzin-Frankel J. The savior cells? Science 2016; 352(6283):284–7
76. Chevrel G, Cimaz R. Osteogenesis imperfecta: new treatment options. Curr Rheumatol Rep 2006;8(6):474–92. 77. Shapiro JR, Rowe DW. Genetic approach to treatment of osteogenesis imperfecta in Osteogenesis imperfecta. 1st ed. London: Elsevier Science and Technology; 2013

READY - MADE CITATION

Doulgeraki A. Osteoporosis of genetic origin: a literature review. *Acta Orthop Trauma Hell* 2023; 74(2): 36-51.