Early-onset osteoporosis: diagnostic and therapeutic implications of *WNT1* variants

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ABSTRACT

Early-onset osteoporosis (EOOP) is a rare but clinically important condition affecting children and young adults, characterized by low bone mass, impaired bone quality, and increased fracture risk. Unlike age-related osteoporosis, which is primarily driven by accelerated bone loss after attainment of peak bone mass, EOOP more often reflects impaired skeletal development, defective peak bone mass acquisition, or primary abnormalities of bone remodeling. While secondary causes must be excluded, a substantial proportion of EOOP cases are now recognized as monogenic in origin. Among these, pathogenic variants in *WNT1* have emerged as a paradigmatic cause of primary EOOP. Heterozygous *WNT1* variants result in autosomal dominant EOOP with variable expressivity, low bone mass, and fragility fractures, frequently associated with low-turnover bone remodeling, whereas biallelic variants cause a severe osteogenesis imperfecta-like phenotype. This review summarizes current concepts in the diagnosis of EOOP, highlighting clinical red flags that should prompt genetic evaluation, and provides an updated synthesis of *WNT1*-related bone fragility, histomorphometric findings, and therapeutic responses reported to date. Emerging evidence suggests that conventional antiresorptive therapies may be suboptimal in *WNT1*-related EOOP, whereas anabolic and Wnt-targeted strategies may represent a more rational approach in selected patients. Persistent gaps in evidence regarding fracture outcomes and long-term management underscore the need for future studies.

KEYWORDS

Early-onset osteoporosis, Wnt signaling, *WNT1*, monogenic osteoporosis, bone fragility.

Introduction

Early-onset osteoporosis (EOOP) refers to osteoporosis occurring in children, adolescents, or adults younger than 50 years, a heterogeneous group of disorders with mechanisms that differ substantially from those underlying age-related osteoporosis. EOOP is clinically important because the associated skeletal fragility, which manifests during growth or early adulthood – when peak bone mass should normally be achieved or recently consolidated – may result in lifelong morbidity. In contrast to postmenopausal osteoporosis, which is predominantly driven by accelerated bone loss, EOOP most often reflects impaired bone accrual, abnormal skeletal modeling, or intrinsic defects in bone quality and remodeling [1,2].

Peak bone mass is a major determinant of fracture risk later in life. Even if secondary insults are corrected in adulthood, it may not be possible to fully reverse disturbances that arose during childhood or adolescence. Fractures sustained during growth may result in vertebral deformities, chronic pain, reduced physical function, and psychosocial burden, highlighting the need for early recognition and appropriate management. Importantly, EOOP should not be regarded simply as "osteoporosis occurring early," but rather as a distinct clinical entity in which developmental and genetic factors play a central role [1,2].

The diagnostic evaluation of EOOP is complex and requires integration of clinical history, fracture pattern, densitometric findings, and laboratory assessment.

Article history

Received 27 Feb 2026 – Accepted 28 Mar 2026

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In children and adolescents, bone mineral density (BMD) must be interpreted using age- and sex-adjusted Z-scores. A Z-score ≤ –2.0 is defined as "low bone mineral density for age and sex" and does not, in isolation, establish a diagnosis of osteoporosis [2,3]. In growing individuals, the diagnosis of osteoporosis requires either a clinically significant fracture history in the presence of low BMD or the occurrence of one or more vertebral compression fractures, irrespective of BMD values [3].

In young adults, reduced BMD (Z-score ≤ –2.0 or T-score ≤ –2.5, depending on skeletal maturity) in combination with low-trauma fractures should prompt investigation for an underlying primary bone disorder [2-4].

Secondary causes—including chronic inflammatory disease, malabsorption, endocrine disorders, hypogonadism, and exposure to glucocorticoids or other osteotoxic medications—must be systematically excluded [1,4]. In the absence of an established chronic disease, secondary factors can be identified in many young individuals presenting with low BMD and fragility fractures; however, when comprehensive evaluation fails to reveal an acquired cause, a monogenic etiology should be

actively considered, and targeted genetic testing is warranted to identify underlying defects in key pathways regulating bone formation and remodeling [1,5].

Over the past decade, advances in next-generation sequencing have fundamentally reshaped the understanding of EOOP. Conditions previously considered idiopathic are increasingly recognized as monogenic disorders affecting key structural and regulatory components of the skeleton [5].

Beyond collagen-related bone fragility disorders, particularly osteogenesis imperfecta caused by mutations in type I collagen genes (*COL1A1* and *COL1A2*), monogenic forms of EOOP also include defects in genes involved in extracellular matrix organization and Wnt/β-catenin signaling, such as *LRP5* (low-density lipoprotein receptor-related protein 5), *WNT1* (Wnt family member 1), and *SOST* (sclerostin), as well as other regulators of osteoblast and osteocyte function [5-10]. Among these, alterations in Wnt/β-catenin signaling have emerged as a central and unifying mechanism in early skeletal fragility. In particular, pathogenic variants in *WNT1* have provided critical insight into the molecular regulation of bone formation and remodeling, establishing *WNT1*-related osteoporosis as a paradigmatic model of monogenic EOOP [6,7].

From a management perspective, this molecular diversity has important clinical implications. Treatment decisions in young patients must carefully balance disease severity against the limited evidence for anti-fracture efficacy of bone-active drugs in this age group, as well as the potential long-term consequences of therapy, including implications for future pregnancy [11].

Early-onset osteoporosis: the diagnostic framework

The diagnostic approach to EOOP begins with careful assessment of fracture history, including age at first fracture, fracture frequency, level of trauma, and skeletal sites involved. Particular attention should be paid to vertebral fractures, which may be clinically silent yet carry major prognostic implications and should be actively sought using spine radiographs or vertebral fracture assessment, especially in patients with back pain, height loss, or unexplained scoliosis [3].

Initial laboratory evaluation includes assessment of calcium–phosphate metabolism, parathyroid hormone, vitamin D status, and bone turnover markers, while endocrine testing should be tailored to the clinical context, and may include thyroid, gonadal, adrenal, and growth hormone axes. Although biochemical parameters may be within reference ranges, this does not exclude a primary skeletal disorder in patients with suggestive clinical features [12].

Clinical "red flags" for a monogenic etiology include onset in childhood or adolescence, recurrent low-trauma fractures, a positive family history of fragility, and limited response to conventional antiresorptive therapy [13]. When no acquired cause is identified after comprehensive evaluation, targeted genetic testing using gene panels or exome sequencing is warranted to enable etiological classification and guide management [5,14].

Chronic inflammatory diseases, malabsorption, endocrine disorders such as hypogonadism or hypercortisolism, and prolonged glucocorticoid exposure represent frequent secondary causes and must be excluded [1,4]. These conditions are often accompanied by systemic manifestations, including growth impairment, delayed puberty, or features of chronic inflammation.

By contrast, primary monogenic forms typically manifest as recurrent fractures in otherwise healthy individuals, often with unremarkable routine laboratory findings [5,13]. The skeletal phenotype may include early vertebral compression fractures, progressive height loss, thin cortices, and reduced trabecular mass, occasionally with disproportionate spinal involvement [15,16]. Underlying mechanisms vary, ranging from high-turnover states in inflammatory or endocrine disorders to low-turnover phenotypes observed in certain genetic conditions such as *WNT1*-related EOOP [15,16]. Recognition of these mechanistic differences is essential, as it may influence both diagnostic interpretation and therapeutic strategy.

Diagnostic interpretation must be adapted to age and developmental stage. In children and adolescents, areal DXA measurements may underestimate volumetric bone density in smaller individuals, whereas vertebral fractures remain a size-independent marker of fragility and should prompt action irrespective of BMD values [3]. In young adults, the coexistence of low BMD and fragility fractures – after exclusion of secondary causes – should raise suspicion for a primary skeletal disorder. Reliance solely on turnover markers is insufficient, as significant structural pathology may occur despite apparently normal biochemical profiles [12,13].

Overall, the expanding recognition of monogenic EOOP has shifted evaluation toward a mechanistic framework of bone fragility, in which disruption of key regulatory pathways – particularly canonical Wnt signaling – plays a central role in skeletal homeostasis.

Table I summarizes the main monogenic disorders associated with early-onset bone fragility, low bone mass, and osteoporosis, together with their key clinical and genetic features.

Wnt signaling and bone biology

Canonical Wnt/β-catenin signaling is a fundamental regulator of skeletal development, osteoblast differentiation, and lifelong bone remodeling. Binding of Wnt ligands to Frizzled receptors and LRP5/6 co-receptors stabilizes β-catenin, promoting transcription of osteogenic target genes and stimulating osteoblast proliferation and differentiation [17]. This pathway is tightly modulated by extracellular antagonists, including sclerostin and Dickkopf-related proteins, which adjust bone formation in response to mechanical and hormonal stimuli.

The biological relevance of Wnt signaling is underscored by human disorders associated with mutations in *LRP5* and *SOST*, leading to low- and high-bone-mass phenotypes, respectively [8,9]. These conditions have demonstrated that Wnt activity influences skeletal strength beyond areal BMD, affecting trabecular microarchitecture, cortical thickness, and material properties of bone.

Among the 19 known Wnt ligands, Wnt1 has emerged as a critical determinant of bone formation. Functional studies show

Table I Key clinical and genetic features of the main monogenic disorders associated with early-onset bone fragility, low bone mass, and osteoporosis.

DISORDER	OMIM / ORPHA	MAIN CLINICAL FEATURES	GENE(S)	INHERITANCE	*KEY REFERENCES*
Osteogenesis imperfecta (classic forms)	OMIM 166200	Recurrent fractures, bone fragility, blue sclerae, dentinogenesis imperfecta, short stature, and skeletal deformities of variable severity; BMD may be variably reduced; possible extraskeletal manifestations (e.g., valvular abnormalities). Most commonly due to variants in type I collagen genes.	*COL1A1* *COL1A2*	AD	Mäkitie, 2019 [5]
WNT1-related osteoporosis	OMIM 615220 615221	EOOP with reduced BMD, vertebral and peripheral fragility fractures, and low-turnover bone remodeling, often with progressive spinal involvement; biallelic variants cause a severe osteogenesis imperfecta-like phenotype with early-onset fractures, skeletal deformities, and growth impairment.	*WNT1*	AD	Laine, 2013 [6] Keupp 2013 [7]
LRP5-related osteoporosis	OMIM 259770 166710	Low BMD with impaired bone accrual and increased fracture risk, often presenting in childhood or early adulthood; variable clinical expressivity ranging from asymptomatic low BMD to early-onset osteoporosis. May be associated with ocular abnormalities such as familial exudative vitreoretinopathy.	*LRP5*	AD / AR	Gong, 2001 [8]
PLS3-related osteoporosis	OMIM 300910	Early-onset low bone mass with recurrent fragility fractures, often involving the spine; typically more severe in males, with variable expression in heterozygous females; normal biochemical markers and absence of major extraskeletal features.	*PLS3*	X-linked	Costantini, 2022 [13]
SGMS2-related osteoporosis	OMIM 126650 616046	EOOP with reduced BMD and recurrent fragility fractures, frequently involving the spine; associated with cranial sclerosis and characteristic calvarial "doughnut" lesions, and possible neurological manifestations (e.g., transient facial nerve palsy).	*SGMS2*	AD	Costantini, 2022 [13]
IFITM5-related osteogenesis imperfecta (type V)	OMIM 610967	Bone fragility with recurrent fractures, hyperplastic callus formation, calcification of interosseous membranes, and radial head dislocation; typically without classical extraskeletal features of osteogenesis imperfecta.	*IFITM5*	AD	Mäkitie, 2019 [5]
SERPINF1-related osteogenesis imperfecta (type VI)	OMIM 613982	Severe bone fragility with recurrent fractures, low BMD, and defective bone mineralization; progressive skeletal deformities and poor response to antiresorptive therapy; absence of type I collagen gene mutations.	*SERPINF1*	AR	Mäkitie, 2019 [5]

Legend: **BMD** = bone mineral density; **EOOP** = early-onset osteoporosis; **AD** = autosomal dominant; **AR** = autosomal recessive

that Wnt1 enhances osteoblast activity, whereas its deficiency compromises skeletal integrity [6,7]. Experimental evidence indicates that this effect is mediated, at least in part, through osteocyte-driven regulation within the bone marrow microenvironment, linking anabolic signaling to coordinated control of bone formation and resorption [18]. Osteocytes integrate mechanical and endocrine cues and regulate surface osteoblast function through controlled expression of sclerostin and other Wnt antagonists [8,9,17,18]. Within this framework, the effects of Wnt1 do not appear to be fully offset by other ligands, providing a mechanistic basis for the marked skeletal fragility observed in *WNT1*-related disorders despite preservation of other pathway components.

Figure 1 shows a schematic representation of the canonical Wnt/β-catenin signaling pathway, highlighting its activation, inhibition, and the consequences of Wnt1 deficiency.

WNT1-related early-onset osteoporosis: genotype–phenotype spectrum

Heterozygous WNT1 variants

Heterozygous pathogenic variants in *WNT1* cause autosomal dominant EOOP with marked phenotypic heterogeneity. Initial reports described large families with EOOP characterized by low BMD, vertebral and peripheral fragility fractures, normal growth, and absence of classical extraskeletal features of osteogenesis imperfecta [19]. Subsequent studies demonstrated that skeletal abnormalities may already be evident during childhood, with impaired peak bone mass acquisition and progressive vertebral involvement [15].

Biochemical markers of bone turnover are frequently within the normal range, yet bone histomorphometry consistently reveals a low-turnover state characterized by reduced osteoblast and osteoclast surfaces and markedly decreased bone formation rates [15,16].

This dissociation between apparently normal laboratory parameters and significant structural skeletal impairment poses a key diagnostic challenge. Even among carriers of the same mutation within a family, phenotypic variability is substantial, ranging from recurrent childhood fractures to osteoporosis diagnosed only in adulthood [20]. Importantly, progressive spinal involvement appears to be a characteristic feature, with increasing kyphosis, vertebral compression fractures, and endplate irregularities reported in adult patients [16]. The absence of vertebral fractures in early stages does not exclude the diagnosis, underscoring the importance of genetic evaluation in clinically suggestive cases [21].

Biallelic WNT1 variants

In contrast, homozygous or compound heterozygous *WNT1* mutations result in a severe osteogenesis imperfecta-like phe-

notype, often classified as osteogenesis imperfecta type XV [6,10]. Affected individuals typically present in infancy with multiple fractures, severe osteopenia, skeletal deformities, and growth failure, and may exhibit neurological manifestations, highlighting the dose-dependent and pleiotropic effects of Wnt1 signaling on skeletal and extraskeletal development.

Histomorphometric and pathophysiological features

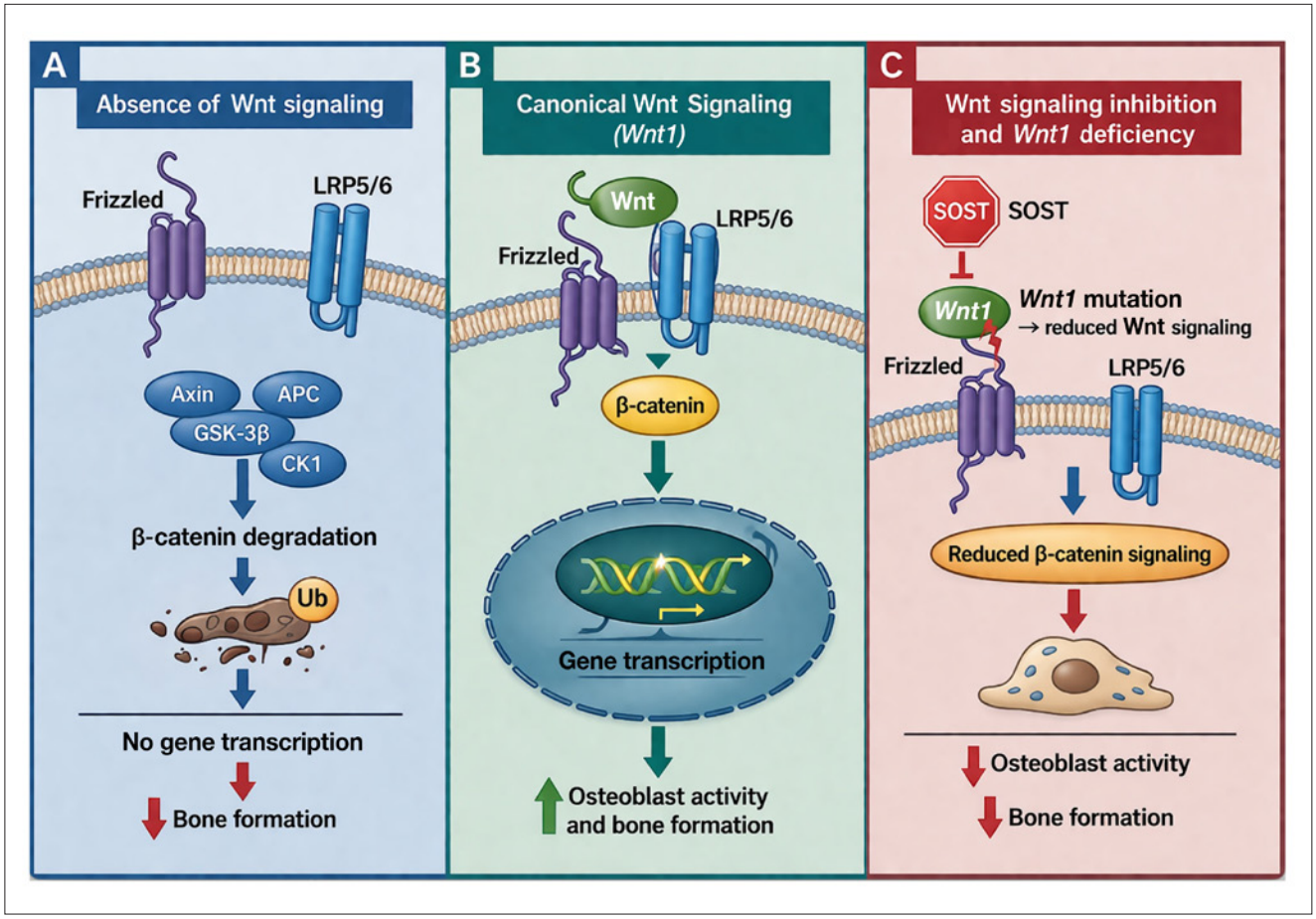
Bone biopsy studies in *WNT1*-related EOOP consistently demonstrate low-turnover osteoporosis characterized by thin trabeculae, reduced osteoblast and osteoclast surfaces, and markedly diminished bone formation rates, while mineralization parameters are generally preserved [15,16]. These findings point to a fundamentally impaired bone formation process, with globally suppressed remodeling limiting the skeleton's adaptive response to microdamage.

Beyond histological evidence of reduced turnover, Wnt1 deficiency alters osteocyte-derived anabolic signaling to osteoblast lineage cells.

Functional studies and animal models indicate that loss of Wnt1 disrupts osteocyte–osteoblast communication, thereby attenuating anabolic drive within the bone microenvironment rather than promoting excess resorption [7,18]. Molecular analyses further support alterations in osteocyte-associated regulatory pathways in Wnt1 signaling disorders [22].

The dissociation between pronounced structural fragility and relatively unremarkable conventional biochemical markers underscores the need for integrated clinical, imaging, and genetic assessment. From a pathophysiological standpoint, *WNT1*-related EOOP exemplifies a disorder of impaired skeletal anabolism, a distinction with important therapeutic implications.

Figure 1 Canonical WNT/ß-catenin signaling pathway in bone and consequences of *WNT1* deficiency.(A) In the absence of WNT signaling, ß-catenin is phosphorylated by the cytoplasmic destruction complex, composed of Axin, adenomatous polyposis coli (APC), glycogen synthase kinase-3ß (GSK-3ß), and casein kinase 1 (CK1), leading to its ubiquitination (Ub) and subsequent proteasomal degradation. As a result, ß-catenin does not accumulate in the cytoplasm and cannot translocate to the nucleus, preventing transcriptional activation of target genes in osteoblast lineage cells and resulting in reduced bone formation.(B) Upon activation of canonical WNT signaling, WNT ligands, including *WNT1* (Wnt family member 1), bind to Frizzled receptors and low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors on the osteoblast membrane. This interaction inhibits the ß-catenin destruction complex, allowing ß-catenin stabilization (i.e., protection from phosphorylation and degradation), cytoplasmic accumulation, and translocation into the nucleus. In the nucleus, ß-catenin interacts with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to promote osteogenic gene transcription, leading to increased osteoblast activity and bone formation.(C) Inhibition of WNT signaling by sclerostin (SOST), a glycoprotein secreted primarily by osteocytes, or reduced *WNT1* signaling due to pathogenic variants (*WNT1* mutation), results in impaired activation of the canonical pathway. Both mechanisms converge on reduced ß-catenin stabilization and nuclear translocation, leading to decreased transcription of osteogenic genes, reduced osteoblast function, and low bone formation, consistent with a low-turnover osteoporosis phenotype.



Therapeutic implications and reported treatment outcomes

Management of EOOP remains challenging, and evidence-based guidelines for monogenic forms are lacking. In *WNT1*-related EOOP, bisphosphonates have shown inconsistent or modest effects on BMD and fracture prevention, particularly in adults, and concerns have been raised regarding potential adverse effects on already suppressed bone remodeling [16,22]. Although bisphosphonates may improve BMD in some patients, their impact on vertebral morphology and long-term fracture risk remains uncertain in this specific context.

The recognition of a low-turnover state in *WNT1*-related EOOP has important therapeutic implications. In this setting, further suppression of bone remodeling through potent antiresorptive agents may yield limited clinical benefit and could theoretically impair microdamage repair over time [16,22]. These considerations highlight the limitations of extrapolating treatment paradigms from postmenopausal osteoporosis to monogenic forms of EOOP and underscore the need for mechanism-based therapeutic strategies. In selected high-risk patients, sequential approaches incorporating an initial anabolic phase followed by consolidation therapy may represent a rational strategy, although robust evidence to guide timing and duration is still lacking [11,23,24].

Anabolic therapies represent a mechanistically appealing alternative. Treatment with teriparatide has been associated with increases in BMD and bone formation markers in adults with *WNT1*-related EOOP, although responses are variable and long-term fracture outcomes remain unknown [23]. Importantly, the anabolic response observed in some patients supports the concept that downstream stimulation of bone formation can, at least partially, overcome upstream signaling defects.

More recently, proof-of-concept evidence has emerged from both experimental models and human case reports supporting the use of sclerostin inhibition. In murine models of Wnt1 deficiency, anti-sclerostin antibodies markedly improved bone mass and reduced fracture rates [18]. In humans, a recent case report described substantial BMD gains following romosozumab treatment in patients with pathogenic variants, suggesting that downstream enhancement of Wnt signaling may partially compensate for upstream defects [24].

Sequential strategies incorporating anabolic therapy followed by antiresorptive consolidation have been proposed for patients at very high fracture risk, but clinical data remain limited [11]. Given the rarity of the condition, therapeutic decisions should be individualized and guided by disease severity, fracture history, and patient-specific factors, ideally within specialized centers. Clinical characteristics and treatment outcomes reported to date in patients with heterozygous *WNT1*-related EOOP are summarized in Table II.

Discussion

WNT1-related EOOP exemplifies how monogenic bone disorders can illuminate fundamental mechanisms of skeletal biology while posing significant diagnostic and therapeutic challenges. Recognition of this entity requires a high index of suspicion and careful integration of clinical, densitometric, and genetic data. The frequent dissociation between normal laboratory findings and severe skeletal fragility highlights the limitations of conventional diagnostic tools in EOOP [12,13,17,22].

From a therapeutic perspective, *WNT1*-related EOOP challenges the traditional antiresorptive-centered paradigm of osteoporosis management. Emerging evidence supports a shift toward mechanism-based strategies, including anabolic and Wnt-targeted therapies, although robust data on fracture reduction, optimal treatment sequencing, and long-term safety are lacking. The establishment of international registries and prospective studies is urgently needed to define clinically meaningful outcomes and inform evidence-based management.

Table II Clinical features and reported treatment outcomes in heterozygous *WNT1*-related early-onset osteoporosis.

STUDY	N	SEX	AGE AT DX	ETHNICITY	WNT1 VARIANT (ZYGOSITY)	SKELETAL PHENOTYPE	BONE TURNOVER HISTOLOGY	ANTI-RESORPTIVE THERAPY	SPECIFIC TREATMENT DETAILS AVAILABLE?	ANABOLIC OTHER THERAPY	REPORTED TREATMENT OUTCOMES
Laine, 2013 [6]	10	M/F	14–68 y	Finnish/ European	Family 1; p.C218G (Het)	Low BMD and multiple low-impact vertebral and peripheral fractures. No extraskeletal abnormalities.	Low-turnover osteoporosis on biopsy	Not reported	No	Not reported	No data reported
Keupp, 2013 [7]	4	M/F	Adolescence to adulthood	European	p.Arg235Trp (Het)	EOOP with recurrent vertebral and rib fractures	Low bone turnover markers	Not systematically reported	No	Not reported	No data reported
Palomo, 2014 [19]	6	M/F	10–61 y	Not reported	Heterozygous (carrier state)	Low BMD in majority; 3/6 with radiographic vertebral compression fractures	Not specifically abnormal	Not reported for carriers	No	Not reported	No data reported

STUDY	N	SEX	AGE AT DX	ETHNICITY	WNT1 VARIANT (ZYGOSITY)	SKELETAL PHENOTYPE	BONE TURNOVER HISTOLOGY	ANTI-RESORPTIVE THERAPY	SPECIFIC TREATMENT DETAILS AVAILABLE?	ANABOLIC / OTHER THERAPY	REPORTED TREATMENT OUTCOMES
Mäkitie, 2016 [15]	8	M/F	10–30 y	Finnish/ European	p.C218G (Het)	EOOP with low BMD, vertebral height loss, pathological fracture history in 4/8, thin diaphyses of long bones, progressive deviation of BMD with age.	Low-turnover osteoporosis on biopsy (n=2); normal mineralization; normal serum turnover markers	Not systematically assessed; one adult subject had prior oral alendronate.	No	Not reported	No systematic treatment data; one adult received prior oral alendronate once weekly for 5 consecutive years (from age 24 to 29 years), with mild lumbar spine BMD improvement (Z-score -2.6 to -2.1).
Mäkitie, 2017 [16]	18	M/F	11–76 y (median 49)	Finnish/ European	p.C218G (Het)	Progressive spinal pathology characterized by vertebral compression fractures, increased thoracic kyphosis, high SDI, Schmorl nodes, and enlarged intervertebral discs. Vertebral compression fractures were present in 39% of subjects overall and in 78% of those aged >50 years.	Not assessed (MRI-based study)	Oral and intravenous bisphosphonates (alendronate, risedronate, zoledronic acid), administered in 9/18 subjects with variable duration (in some cases ≥5 years); 4/18 received PTH analogs and 1/18 denosumab as part of sequential therapy, based on individual patient data.	Yes (individual treatment histories reported; no standardized protocol)	PTH analogs and denosumab in subset; estrogen therapy in one subject	High prevalence of vertebral compression fractures (39%; 78% in subjects >50 yrs) and progressive spinal deformities; the study was not designed to evaluate the anti-fracture efficacy of the therapies.
Alhamdi, 2018 [20]	4	M/F	10–80 y	Not reported	p.Trp351Arg (Het)	EOOP; vertebral fractures absent in some carriers	Functional impairment of canonical Wnt signaling	IV zoledronic acid in proband only (3 infusions over 14 months)	Yes	None	Lumbar spine Z-score improved from -3.2 to -2.5 and whole-body Z-score from -2.2 to -1.6 after 3 zoledronic acid infusions (14 months); no vertebral fractures reported in the family; fracture outcomes not systematically evaluated.
Campopiano, 2022 [21]	1	F	35 y	Caucasian	p.Leu370Val (Het)	Multiple acute vertebral fractures postpartum	Low–normal turnover	None before diagnosis	Yes	Teriparatide 20 µg/day ×24 months	Lumbar spine BMD +14.6%, femoral neck +8.3%, total hip +4.9% after 24 months of teriparatide; no additional clinical or vertebral fractures during follow-up.

STUDY	N	SEX	AGE AT DX	ETHNICITY	WNT1 VARIANT (ZYGOSITY)	SKELETAL PHENOTYPE	BONE TURNOVER HISTOLOGY	ANTI-RESORPTIVE THERAPY	SPECIFIC TREATMENT DETAILS AVAILABLE?	ANABOLIC OTHER THERAPY	REPORTED TREATMENT OUTCOMES
Välimäki, 2017 [23]	3	M/F	49–72 y	Finnish/ European	p.C218G (Het)	EOOP with multiple vertebral compression fractures	Low turnover	All patients had prior exposure to bisphos-phonates	No	Teriparatide 20 µg/day ×24 months	Lumbar spine BMD increased ~5–8%; no new clinical fractures; one new mild morphometric vertebral compression.
Cavalcanti Matos, 2025 [24]	1	F	28 y	Not reported	Frameshift (Het)	Severe EOOP with vertebral and rib fractures	Not available	Denosumab (add-on to teriparatide for ~10 months; resumed after romoso-zumab)	Yes	Sequential therapy: Teriparatide 20 µg/day (24 months) with add-on denosumab 60 mg every 6 months after 14 months (overlap); followed by romoso-zumab 210 mg monthly (12 months) and subsequent denosumab resumption (60 mg every 6 months).	Marked BMD gains (lumbar spine +42.1%, total hip +16.6%) after sequential teriparatide, denosumab, and romoso-zumab; fracture-free for >4 years of follow-up.

Legenda: **BMD** = bone mineral density; **EOOP** = early-onset osteoporosis; **AD** = autosomal dominant; **AR** = autosomal recessive

Conclusions

Early-onset osteoporosis is a heterogeneous condition in which monogenic defects are increasingly recognized as key drivers of skeletal fragility. *WNT1*-related bone fragility represents a paradigmatic form of EOOP characterized by impaired Wnt signaling, low bone turnover, and variable clinical expression. Advances in genetic diagnostics have improved recognition of this disorder, while emerging anabolic and Wnt-targeted therapies offer promising new management options. Continued collaborative research is essential to translate these insights into evidence-based care for affected patients.

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Acknowledgments: *BOND ERN, Bone Metabolic Unit, Careggi University Hospital, Florence, is a member of BOND ERN.*
Conflicts of interest statement: *The author declares no conflicts of interest.*