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Case Report

A Novel Biallelic Variant in The *SERPINH1* Gene in Two Siblings Diagnosed with Osteogenesis Imperfecta Type X: Evidence of Intrafamilial Clinical Variability

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What is already known on this topic?
SERPINH1 encodes heat shock protein 47 (HSP47), a collagen-specific chaperone essential for proper type I collagen folding. Biallelic pathogenic variants in *SERPINH1* cause osteogenesis imperfecta type X, an exceedingly rare autosomal recessive form of OI with only a limited number of cases reported worldwide.

What this study adds?
This study provides the first detailed documentation of intrafamilial phenotypic variability in SERPINH1-related OI and adds further evidence supporting genotype–phenotype diversity among Turkish patients.

Abstract
Osteogenesis imperfecta (OI) is a genetically and phenotypically heterogeneous group of disorders primarily characterized by bone fragility, impaired growth, and skeletal deformities. Although OI was historically attributed to monoallelic pathogenic variants in *COL1A1* and *COL1A2*, recent advances have identified autosomal recessive forms caused by defects in genes involved in collagen biosynthesis and processing. *SERPINH1* encodes heat shock protein 47 (HSP47), a collagen-specific molecular chaperone essential for proper folding of the procollagen triple helix and its transport to the Golgi apparatus. Loss-of-function variants in *SERPINH1* cause OI type X, a rare autosomal recessive form associated with moderate to severe bone fragility. We evaluated two Turkish siblings with clinical features of OI, including short stature, recurrent fractures, low bone mineral density, and skeletal deformities. Exome sequencing identified a novel homozygous missense variant in *SERPINH1* (NM_001235.5: c.250G>C; p.G84R) in both siblings. Despite sharing the same genotype, they exhibited marked intrafamilial phenotypic variability: the 8-year-old brother presented with early-onset, severe skeletal manifestations, whereas his 11-year-old sister showed a milder, later-onset phenotype.
This report expands the genotypic and phenotypic spectrum of SERPINH1-related OI, highlights intrafamilial variability, and adds further data on Turkish patients with this rare condition.
Keywords: bone fragility, low bone mass, osteogenesis imperfecta, *SERPINH1*

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1. Introduction:

Osteogenesis imperfecta (OI), or "brittle bone disease," is a heritable connective tissue disorder characterized by bone fragility, skeletal deformities, and recurrent fractures, with an estimated incidence of 1 in 15,000–20,000 live births (1). The classification proposed by Sillence et al. in 1979 defined four major clinical types: type I (mild), type II (perinatally lethal), type III (severe but non-lethal), and type IV (moderate severity) (2). Advances in molecular genetics have since expanded and refined this system, identifying additional subtypes and highlighting the extensive clinical and genetic heterogeneity of the disorder (3). Beyond skeletal involvement, affected individuals may present with extra-skeletal features such as blue sclerae, joint hypermobility, dentinogenesis imperfecta (DI), hearing loss, and, in some cases, cardiovascular or respiratory complications (4). Approximately 90% of patients harbor heterozygous pathogenic variants in *COL1A1* (MIM #120150) and *COL1A2* (MIM #120160), encoding the α1(I) and α2(I) chains of type I collagen, respectively (5, 6). In the past two decades, additional causative genes have been identified in both dominant and recessive forms of OI, implicated in processes including post-translational modification of type I procollagen, osteoblast-specific signaling, and transcriptional regulation (7, 8). The post-translational modification and proper folding of type I procollagen require the coordinated activity of modifying enzymes, for example, prolyl hydroxylases, together with several endoplasmic reticulum (ER)–resident chaperone proteins (9). Among these, heat shock protein 47 (HSP47) is a collagen-specific molecular chaperone localized in the ER that ensures correct folding of collagen chains (10, 11). HSP47 binds directly to the triple helix region of procollagen molecules after their initial modification by the prolyl 3-hydroxylation complex. It is encoded by the *SERPINH1* gene (serpin family H member 1), in which biallelic pathogenic variants cause OI type X (MIM #613848) (12) . HSP47 stabilizes the folded procollagen structure, prevents intracellular degradation, inhibits aggregation of nascent collagen chains, and facilitates transport from the ER to the Golgi apparatus. The essential role of HSP47 is underscored by embryonic lethality in Hsp47-knockout mice (13). In humans, SERPINH1-related OI type X is exceedingly rare, typically presenting with moderate to severe phenotypes, and in some cases, perinatal lethality. Here, we report two siblings harboring a novel homozygous missense variant in *SERPINH1*, both with a moderate to mild OI type X phenotype. Notably, the male sibling exhibited more severe skeletal manifestations than his sister, illustrating intrafamilial phenotypic variability in SERPINH1-related OI.

2. Materials and Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki. Institutional review board (IRB) approval was obtained for this retrospective study from the Non-Invasive Clinical Research Ethics Committee of the University of Health Sciences, Diyarbakır Gazi Yaşargil Training and Research Hospital (Approval Number: 171). Written informed consent was obtained from participants or from the parents/legal guardians of minors.

3. Clinical report:

Case 1

The proband, a 5-year-8-month-old boy and the third child of healthy, non-consanguineous parents from the same village, was born at term following an uneventful pregnancy, with unremarkable prenatal ultrasonography. His first fracture occurred shortly after achieving independent ambulation on the right femora, precipitated by a minor fall. At presentation, he was referred for evaluation of disproportionate short stature and progressive kyphosis, first noted at four years of age. Anthropometric measurements demonstrated a height SDS of –2.1, weight SDS of –1.5, and head circumference SDS of –1.0. Physical examination revealed relative macrocephaly, laxity of the metacarpophalangeal and elbow joints, short neck, prominent jaw, broad and short trunk, pectus carinatum, and pes planus (Fig. 1b). Radiographic assessment showed rib cupping, thoracic kyphosis, reduced lumbar lordosis, generalized osteopenia, codfish vertebrae, and severe platyspondyly in the thoracic and upper lumbar spine (Fig. 2a). Additional findings included coxa valga, mild bowing of the femora, and metaphyseal widening of the lower extremities (Fig. 2b, c). Audiological, ophthalmological, and echocardiographic evaluations were normal. Lumbar spine bone mineral density (BMD) (L1–L4) Z-score was –5.1. Serum calcium, phosphate, alkaline phosphatase, and vitamin D concentrations were within reference ranges. He sustained five additional low-trauma long bone fractures (right humerus and ulna, left radius, and bilateral femora) prior to the initiation of intravenous pamidronate therapy. (1 mg/kg every three months). After two years of treatment, at eight years of age,, his height SDS improved to –1.7, weight SDS to –1.3, and lumbar spine BMD Z-score to –2.1. No additional fractures occurred during therapy, and he did not require any surgical interventions.**Case 2**:

His 12-year-old sister was evaluated for disproportionate short stature, recurrent fractures, and a family history. She had sustained a low-trauma left femoral fracture at age 10 and a right distal radius fracture at age 11. At nine years of age, her height and weight SDS were –1.2 and –2.0, respectively; by 11 years 5 months, her height SDS had declined to –2.0, while her weight SDS remained at –1.9. Physical examination was notable for webbed neck, shield chest with a pectus carinatum deformity (Fig. 1c). Neurodevelopmental milestones and cognitive assessments were within normal limits. Audiological and ophthalmological evaluations yielded no abnormalities. Abdominal ultrasonography was normal, whereas echocardiography revealed mitral valve prolapse with associated regurgitation. Due to short stature, webbed neck, and shield chest, karyotype analysis was conducted to exclude Turner syndrome and revealed a normal female karyotype (46,XX).Lumbar spine BMD (L1–L4) Z-score was –3.3 at age 11 and declined further to –3.8 at age 12. Skeletal survey demonstrated generalized osteopenia of the lumbar vertebrae with preserved vertebral body heights and mild osteopenia of the long bones (Fig. 1g–i). Given her history of recurrent fractures and progressive decline in BMD, intravenous BP therapy was initiated. At the time of reporting, following six months of treatment, she remained free of new fractures.

3.1. Orodental Findings

In Case 1, maxillary second primary molars had severe crown destruction with possible pulpal involvement; mandibular incisors showed yellowish-brown discoloration, irregular surface texture, and poor translucency (Fig. 2 a, b). Mild crowding, calculus, and delayed dental maturation were noted. Maxilla and mandible were osteopenic radiographically (Fig. 2 c). Case 2 had localized gray discoloration of mandibular permanent incisors. No clear radiographic evidence of DI was observed in either sibling.

3.2. Molecular analysis

Exome sequencing (ES) was performed to identify the molecular etiology (Supplementary Data 1). A novel biallelic missense variant in *SERPINH1* (NM_001235.5: c.250G>C; p.G84R) was detected in the proband and his affected sister (Fig. 3 a- b). The identified variant was classified as likely pathogenic following the American College of Medical Genetics and Genomics (ACMG) guidelines, fulfilling the PM2 and PP3 criteria. (14). It was absent from major population databases, including gnomAD, ExAC, and the 1000 Genomes Project, and was not reported in public variant databases such as ClinVar and HGMD. Furthermore, multiple in silico prediction tools, CADD, PolyPhen-2, SIFT, and MutationTaster consistently predicted a deleterious effect on protein function, supporting the PP3 criterion (Fig. 3 c-d). The variant was present in the heterozygous state in both parents, confirming autosomal recessive inheritance. The clinical and radiologic findings of the present and previously reported patients are summarized in Table 1.

4. Discussion:

Osteogenesis imperfecta type X (OI, Type X; MIM # 613848) is a rare recessive form of OI caused by biallelic variants in the *SERPINH1* gene. To date, around 17 distinct *SERPINH1* variants have been reported in the literature (https://www.lovd.nl/). Among these, eleven variants in the biallelic state are definitively implicated in OI type X. These eleveneinclude eight missense variants (p.L78Pro, p.L50R, p.M237T, p.E212A,p.R222S, p.D385N, p.R405H, p.G411S), two frameshift variants (c.338_357delins22, c.1233dupT), and one in-frame deletion (c.314_325del) affecting an essential HSP47 domain, predicted to alter chaperone function (12, 15-20). An additional structural variant, a large upstream deletion that downregulates SERPINH1 expression, has also been identified in two affected siblings in trans with a frameshift allele (19). Phenotypic severity among the 11 reported individuals with biallelic *SERPINH1* variants spans from perinatal-lethal OI to moderately severe, survivable forms (15-20). Prenatally manifesting cases typically present with multiple intrauterine fractures, marked skeletal undermineralization, and respiratory insufficiency, often resulting in perinatal death (12, 15, 20). In contrast, milder cases survive well into adulthood, presenting with a moderate to severe OI phenotype characterized by short stature, low BMD, recurrent fractures, and bowing of the long bones. Loss-of-function (LoF) *SERPINH1* variants are consistently associated with the most severe, early-onset phenotypes, often lethal in the perinatal period. For example, a homozygous frameshift variant (c.338_357delins22, p.E113Vfs*8) that abolished HSP47 production was reported in a newborn who presented with multiple fractures at birth and died within days, representing a lethal OI outcome (15). Similarly, in two siblings compound-heterozygous for a frameshift allele and a large upstream deletion (which drastically reduced SERPINH1 expression), the resulting HSP47 deficiency led to a severe, albeit non-lethal, OI phenotype. Notably, the presence of the partial-expression deletion in that case may have permitted some residual HSP47 production, tempering the clinical severity compared to a complete null allele (19). In line with these observations, missense variants in *SERPINH1* typically allow production of an HSP47 protein that is structurally altered but partially functional, and affected individuals generally show moderate-to-severe OI (12, 16, 17, 21). These variants usually impair HSP47's stability or collagen-binding capacity rather than eliminating the protein entirely. For instance, the L78P variant, the first human *SERPINH1* missense OI variant identified, causes HSP47 to misfold and undergo proteasomal degradation, drastically reducing HSP47 levels in patient fibroblast (12). This results in a severe OI phenotype, albeit survivable (OI type III). In contrast, the p.Met237Thr (M237T) substitution has a milder biochemical effect: patient fibroblasts retain approximately 50% of normal HSP47 levels. Although the M237T mutant protein is partially mislocalized within the ER, collagen folding and post-translational modification remain largely normal. In general, most HSP47 missense variants do not cause collagen "overmodification," as HSP47 functions after the initial prolyl 3-hydroxylation and glycosylation steps, and its loss does not substantially prolong collagen's exposure to modifying enzymes (16). An important exception to this rule is the recently reported p.Arg222Ser (R222S) variant. Crystal-structure studies have identified several histidines (His215/216, His238, His273/274, and His386) as key contributors to the pH-dependent HSP47–collagen interaction(22). Although residues such as Glu212, Arg222, Met237, and Asp385 are not themselves histidines, they lie within or adjacent to this structurally defined surface. Based on their proximity to experimentally validated contact residues and their predicted influence on local electrostatics or loop conformation are expected to impact the collagen-binding interface. However, for these positions, aside from Arg222, direct biochemical evidence is not yet available, and the interpretation is therefore based on structural modelling and pathogenic phenotype correlation rather than functional assays.R222S variantlies in HSP47's collagen-binding interface and was identified in a child with perinatal-onset, lethal OI. Uniquely, the HSP47-R222S protein is produced at normal levels and is correctly localized, but it exhibits markedly reduced affinity for type I collagen (20). As a result the procollagen ends up abnormally over-modified. Syx et al. demonstrated that this

paradoxical over-modification occurs because other ER chaperones and modifying enzymes become upregulated and abnormally bind to procollagen when HSP47 cannot bind, compensating for HSP47's loss but inadvertently increasing collagen modifications. In other words, a defect in HSP47's collagen-binding site can trigger a cascade of compensatory interactions that overshoot, leading to collagen that is "over-processed" despite a normal folding timeline (20). This phenomenon, observed only with the R222S mutant so far, suggests that mutations directly disrupting HSP47's binding to collagen may have an additive deleterious effect beyond the typical LoF, potentially explaining the especially severe phenotype in that case. It also echoes the principle seen in dominant OI that substitutions of critical glycine residues in collagen by small amino acids produce widely variable, often severe outcomes. Variants affecting the HSP47–collagen interface might similarly exacerbate clinical severity compared to variants in the non-binding region (12, 21). In 2024, Aliyeta et al. described two individuals carrying pathogenic variants in the SERPINH1 gene: one homozygous for p.E212A and another compound heterozygous for p.D385N and p.G411S. The patient harboring the homozygous p.E212A variant, which lies within the collagen-binding interface of HSP47, presented with a severe OI phenotype. In contrast, the individual carrying the compound heterozygous variants (p.D385N and p.G411S) exhibited a milder phenotype. Although p.D385N also resides within the collagen-binding region, the trans-configuration with p.G411S—a variant outside the binding interface—likely allowed residual HSP47 function, resulting in partial preservation of collagen processing and a less severe clinical course (21). The present report adds a novel missense variant, p.Gly84Arg (G84R), to the spectrum of *SERPINH1* variants. This substitution occurs in the N-terminal portion of HSP47's serpin domain, a region that is highly conserved and crucial for proper folding of the chaperone. Although we did not perform functional assays, the variant's location within the conserved N-terminal serpin domain and outside the direct collagen-binding interface suggests that p.G84R is unlikely to cause collagen "overmodification." Instead, by analogy to the nearby p.L78P substitution, it most likely destabilizes the HSP47 fold, reducing the steady-state level of functional chaperone without altering collagen post-translational modification. Consistent with this, the clinical observations in our two sibling patients indicate a partial loss-of-function: both children are moderately affected, yet notably survived the perinatal period and infancy, and even show intrafamilial variation in severity. The younger brother has a more typical moderate to severe OI presentation from early childhood, whereas his older sister exhibits a later-onset, milder course despite carrying the same genotype. This suggests p.G84R permits enough residual HSP47 function to avoid the most extreme outcomes, aligning with other *SERPINH1* missense cases. Overall, the G84R cases reinforce the emerging genotype–phenotype trend: even among siblings with identical *SERPINH1* variants, differences in residual HSP47 activity, potentially influenced by additional genetic or environmental modifiers, can markedly alter disease severity. This variability likely reflects the specific impact of each variant on protein stability, collagen-binding affinity, and subsequent collagen post-translational processing. Table 2. summarizes the biochemical consequences and phenotypes of reported HSP47 defects.

Over the past two decades, bisphosphonates (BPs) have become a mainstay for improving bone density and reducing fracture risk in OI patients. These anti-resorptive drugs inhibit osteoclast activity, leading to increased BMD and, in many cases, fewer fractures. However, most data on BP efficacy come from dominant (COL1A-related) OI or small case series, and specific evidence in OI type X (SERPINH1-related) is limited given the rarity of the condition (17, 23). Clinical studies have shown that BPs improve BMD and reduce fracture incidence, although most data are derived from small cohorts, limiting generalizability. In the context of SERPINH1-related OI, BP therapy has been reported in only a few patients, with generally favorable effects on BMD. However, data on fracture outcomes remain limited (24, 25). In one report, a patient who received seven years of BP treatment (initially alendronate followed by zoledronic acid) showed marked improvement in BMD and reduced fracture frequency, particularly during the intravenous zoledronate phase (17). Another case described persistent fractures despite six years of pamidronate, later transitioning to zoledronate; fracture rates decreased after puberty, although the effect of treatment versus natural disease course could not be distinguished (19). In comparison, P1 in our cohort received two years of pamidronate, which resulted in improved BMD and no fractures during treatment. In contrast, P2 underwent only six months of therapy; her BMD declined slightly, yet she did not sustain any fractures. These observations suggest that BPs may be beneficial in managing skeletal fragility in SERPINH1-related OI; however, outcomes appear variable and may depend on timing, duration, and type of agent used. Further studies involving larger cohorts and longer follow-up are required to establish standardized treatment protocols and assess long-term skeletal outcomes in this rare OI subtype.

Study limitations

We could not perform laboratory analyses (e.g protein expression, collagen-binding studies) to directly assess how the p.G84R mutation alters HSP47 function. This limits our mechanistic insight into the molecular basis of intra- and interfamilial variability observed. BP therapy was administered for only a short period, limiting assessment of potential long-term benefit. The rarity of this OI subtype also restricted the scope for definitive genotype–phenotype correlations.

Conclusion

Null SERPINH1 variants that eliminate HSP47 function have been associated with perinatal-lethal OI, whereas non-null variants exhibit a broad range of clinical presentations. Missense changes that disrupt the collagen-binding interface tend to produce the most severe survivable phenotypes, while variants outside this region or those primarily affecting protein stability generally preserve partial chaperone activity and result in clinically heterogeneous but non-lethal forms of OI. The phenotypic differences observed in our patients highlight the contribution of residual HSP47 function and the possible influence of additional genetic or environmental modifiers. Further well-characterized cases and functional studies are needed to more precisely define genotype–phenotype relationships in this rare OI subtype.

Data availability

The data supporting this study's findings are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Health Sciences, Diyarbakir Gazi Yasargil Training and Research Hospital Noninvasive Clinical Research Ethical Committee (approval number: 2024/171).

Consent to participate: Written informed consent was obtained from the parents.

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Author Contributions

Conceptualization; Akçahan Akalın; Data curation; Akçahan Akalın, İsmet Rezani Toptancı, Ruken Yıldırım, Formal analysis; Akçahan Akalın ; Investigation; Akçahan Akalın, İsmet Rezani Toptancı, Şervan Özalkak, Methodology; Akçahan Akalın, Ruken Yıldırım; Project administration; Akçahan Akalın, İsmet Rezani Toptancı; Resources; Akçahan Akalın, İsmet Rezani Toptancı, Ruken Yıldırım; Software; Akçahan Akalın Supervision; Şervan Özalkak, Ruken Yıldırım Validation; Akçahan Akalın, İsmet Rezani Toptancı, Ruken Yıldırım; Visualization; Roles/Writing - original draft; Akçahan Akalın, İsmet Rezani Toptancı, Ruken Yıldırım, Writing - review & editing: İsmet Rezani Toptancı, Ruken Yıldırım.

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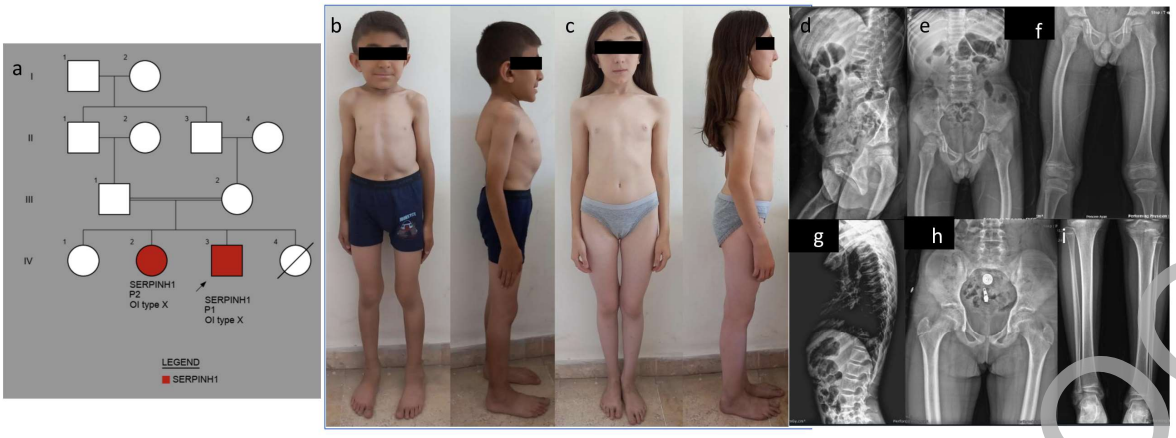

Fig 1. Pedigree illustrating the proband (P1) and his affected sister (P2) (a). Clinical photograph of P1 at 8 years of age, showing a short neck, relative macrocephaly, prominent chin, grey-blue sclerae, pectus deformity, and kyphoscoliosis (b). P2 at 12 years of age, with no notable skeletal abnormalities apart from short stature, webbed neck and pectus carinatum deformity (c). Plain radiographs of Patient 1 (P1) at 6 years of age showing platyspondyly, marked osteopenia, and vertebral body compression (d), and pelvic views demonstrating generalized osteopenia, bilateral coxa valga deformity, mild bowing of the femora, and metaphyseal widening at the distal femur (e–f). . Radiographic findings in P2 at 11 years of age. Lateral spine radiograph demonstrated osteopenia in the thoracolumbar region; however, vertebral body heights were preserved (g). Anteroposterior pelvic radiograph revealed generalized osteopenia, bilateral mild coxa valga deformity, shallow acetabular roofs, metaphyseal irregularities of the proximal femora, hypoplastic iliac wings, and an underdeveloped sacrum (h). Anteroposterior radiograph of the lower legs showed gracile tibiae and fibulae with diffuse osteopenia, mild anterior bowing, and metaphyseal irregularities (i).

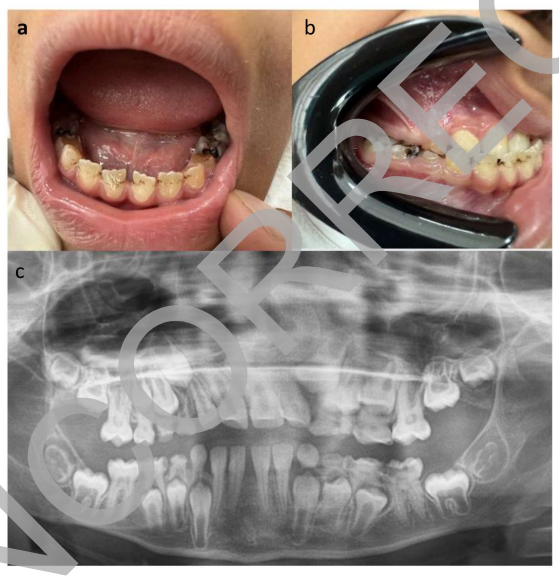

Fig 2. Intraoral examination of the P1. Extensive dental plaque and extrinsic brown pigmentation in the anterior mandibular teeth (a). Multiple carious lesions were noted, most prominently in the maxillary second primary molars, which exhibited extensive crown destruction and possible pulpal involvement (b). The image shows mixed dentition with delayed development of permanent tooth buds and root formation. The maxillary and mandibular bones appear osteopenic, with sparse trabeculation and thin cortices. There are no radiographic features consistent with dentinogenesis imperfecta (DI). Mild anterior crowding and dental calculus were observed in the mandibular arch (c).

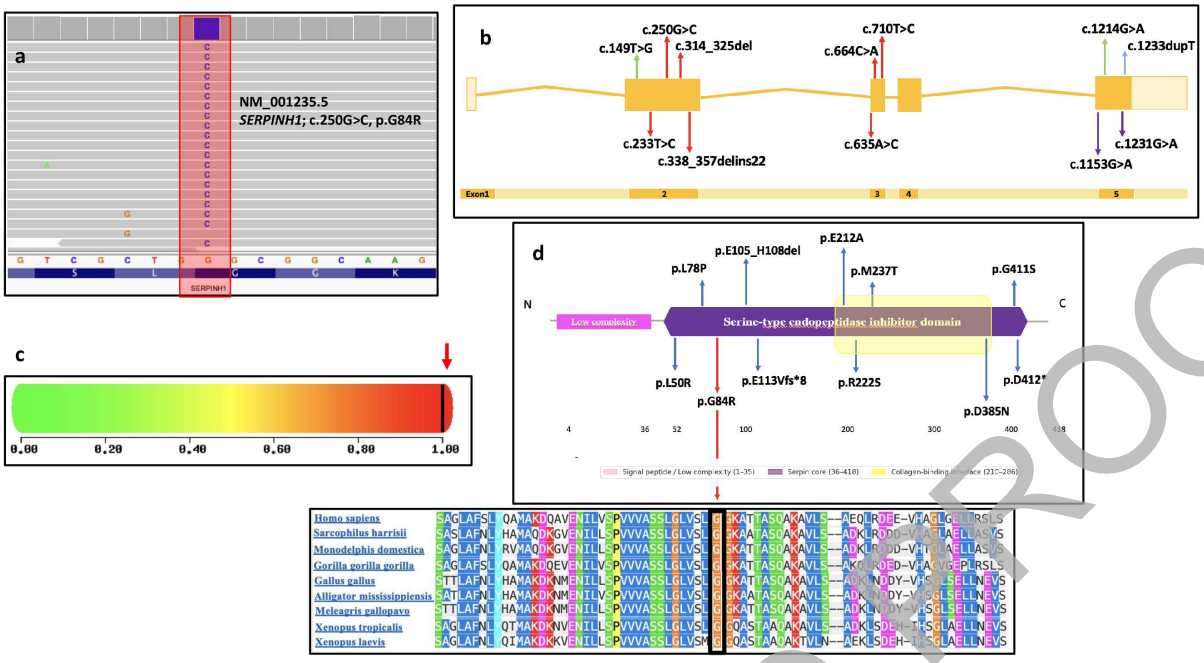

Fig 3. IGV visualization of the variant detected in the *SERPINH1* gene (a). Schematic representation of *SERPINH1* variants reported to date, including those identified in the present study. Most pathogenic variants are clustered in exon 2; however, additional disease-associated alterations are distributed throughout the gene. Green and purple arrows denote compound heterozygous variants. Blue arrow indicates pathogenic allele in trans with an upstream deletion. Red arrows represent homozygous variants (b). The biallelic missense variant detected in the present study is predicted to be probably damaging with a score of 1.00 by the Polyphen prediction tool (c). Schematic representation of the HSP47 (SERPINH1) protein and evolutionary conservation of OI-associated variant sites. The low-complexity/signal peptide region (pink) and the serine-type endopeptidase inhibitor (serpin) core domain (purple) are indicated, with the collagen-binding interface (residues 210–386) highlighted in yellow. Previously reported OI-associated variants are shown by blue arrows, while the novel variant identified in this study (p.G84R) is marked in red. The mapped variants are distributed across the protein: some cluster in the N-terminal segment (potentially affecting protein folding or stability), others fall within the collagen-binding site, and others occur near the C-terminus, possibly impacting the serpin reactive loop or overall conformation. Below, a multiple sequence alignment of HSP47 orthologs from several vertebrate species demonstrates strong conservation at residues affected by OI-associated variants. Sequence alignment of vertebrate HSP47 proteins showed that Glysin84 (G84) is highly conserved (d).

Table 1. A comparison of the clinical, radiological, and molecular genetic findings between previously reported patients and the present cases

Reference	**Present study**		**Christiansen et al. (2010)**	**Duran et al. (2015)**		**Marshall et al. (2016)**	**Essawi et al. (2017)**	**Song et al. (2018)**
	F1		F2	F3		F4	F5	F6
	P1	P2	P3	P4	P5	P6	P7	P8
Sex	M	F	M	F	M	M	M	M
Origin	Turkish		Saudi	N/A N/A		Mexico	Palestinian	Chinese
Consanguinity	First cousin		First Cousin	Third cousin		None	+	None
Genetic alteration (*SERPINH1* NM_001235.5)	c.250G>C, p.G84R		c.233T>C, p.L78P	c.710T>C, p.M237T		c.338_357delins22, p.E113Vfs*8	c.314_325del; p.E105_H108del	c.149T>G, p.L50R/c.1214G>A, p.R405H
Inharitance	Homozygous		Homozygous	Homozygous		Homozygous	Homozygous	Compound heterozygous
Severity of the disease	Moderate severity (OI type III)	Mild (OI Type IV)	Severe (OI type III-early demise)	Moderate severity (OI type III)		Severe (OI type II-lethal phenotype)	Moderate severity (OI type III)	Moderate severity (OI type III)

Antenal ultrasonography findings	N	N	Short bowed femora, low calvarial echogenicity, and a relatively small chest	N/A	N/A	Ascites, plevral effusion, short long bones,ventriculomegaly	N/A	N/A
Requiring NICU after birth	None		MV support+	N/A	N/A	MV support+	N/A	N/A
Age on set of symptoms	After walking around 2 years old	10 year	Birth (Multiple rib fractures, bilateral humeral fractures, and platyspondyly)	4	6 months	Birth (Multiple fractures of the ribs, flexed abducted right hip, short and bowed limbs, facial dysmorphism	N/A	3
Age on set of fractures (years)	2	10	Birth	4	6 months	Birth	2	3
Number of fractures	5	4	Multiple+	N/A (Vertebral, femur fractures)	N/A (Vertebrae compression fractures)	Multiple+	4	8
Long bone fractures	+	+	+	+	-	-	Type of the fractures were not reported	+
Vertebral compression fractures	+	-	-	+	+	Marked compression		Marked compression
Rib fractures	-	-	+	-	-	+		+
Dysmorphic features								
Relative macrocephaly	+	+	+	N/A	N/A	+	N/A	N/A
Large anterior fontanel	N/A	N/A	+	+	+	+	N/A	N/A
Short neck	+	+	-	N/A	N/A	+	N/A	N/A
Triangular face	+	+	+	N/A	N/A	+	N/A	N/A
Short nose	-	-	-	N/A	N/A	+	N/A	N/A
Prominent chin	+	+	-	N/A	N/A	-	N/A	N/A
Microretrognathia	-	-	+	N/A	N/A	+	N/A	N/A
Blue sclera	+	+	+	-	-	+	+	-
Shortened of long bones	-	-	+	N/A	N/A	+	N/A	-
Pectus deformity	Pectus carinatum	Pectus carinatum	Pectus carinatum	N/A	N/A	N/A	+	N/A
Narrow chest	-	-	+	+	+	+	N/A	N/A
Joint hypermobility	+	-	Generalized +	+	+	+	+	N/A
Kyphoscoliosi / scoliosis	+	-	+	-	+	N/A	-	-
Short stature	+	+	+	N/A	N/A	+	N/A	+
Hearing loss	-	-	N/A	-	-	N/A	-	-

Radiologic featues								
Wormian bones	-	-	-	+	+	-	N/A	+
Thin ribs	+	+	+	+	+	+	N/A	N/A
Platyspondyly	+	-	+	-	+	+	N/A	+
Bowing of the long bones	+	-	+	+	+	+	N/A	+
Coxa valga deformity	+	+	-	+	+	-	N/A	+
Generalized osteopenia	+	+	+	+	+	+	+	+
Orodental features	Dental crowding, discolorotion, DI(-)	Discoloration, DI(-)	DI (+)	DI (-)	DI (-)	N/A	DI (+)	DI (-)
ID/DD	N	N	DD	N/A	N/A	Generalized hypotonia	DD	N/A
Treatment (duration)	Pamidronate 2 years continued+ vitamin D3 (400 units)	Pamidronate 6 months continued + vitamin D3 (400 units)	Pamidronate 2 years + vitamin D (800 units) + elemental calcium (2 weeks)	N/A	N/A	-	N/A	Oral aledronate-3 years/ zoledronate-4years
BMD Z score before treatment	-5.1	-3.8	Increased BMD after treatment	N/A	N/A	-	N/A	-5.3
BMD Z score after treatment	-2.1	-		N/A	N/A	-	N/A	0.9
Decreased of fracture numbers after treatment	+ (No fracture observed after treatment)	+ (No fracture observed after treatment)	N/A	N/A	N/A	-	N/A	+
Other comorbidities	-	MVP+MI	Kidney Stones, pelviureteric junction obstruction, hydronephrosis, loss of renal function, recurrent low tract infections, subdural hematoma Deceased at age 3.5 years	-	-	Hydranencephaly, right undescended testis, deceased at potnatal 8th day	Wheelchair	-

Table 1. continued

Reference	**Schwarze et al. (2019)**		**Syx et.al (2021)**	**Aliyeva et.al (2024)**	
	F7		F8	F9	F10
	P9	P10	P11	P12	P13
Sex	F	M	F	F	M
Origin	N/A	N/A	Indian	Turkish	Turkish

Consanguinity	None		None	+	None
Genetic alteration (*SERPINH1* NM_001235.5)	c.1233dupT, p.D412*/ deletion upstream of *SERPINH1*		c.664C>A, p.R222S	c.635A>C, p.E212A	c.1231G>A, p.G411S/ c.1153G>A, p.D385N
Inharitance	Compound heterozygous		Homozygous	Homozygous	Compound heterozygous
Severity of the disease	Modarete to severe (OI type III)		Severe (OI type III-early demise)	Severe (OI type III)	Mild (OI type I)
Antenal ultrasonography findings	N/A	N/A	N/A	N/A	N/A
Requiring NICU after birth	N/A	N/A	N/A	N/A	N/A
Age on set of symptoms	birth	birth	birth	2 years	2 years
Age on set of fractures (years)	birth	birth	birth	2 years	2 years
Number of fractures	33	15	Multiple+	Multiple+	Multiple+
Long bone fractures	+	+	+	+	+
Vertebral compression fractures	+	-	+	N/A	N/A
Rib fractures	+	+	+	N/A	N/A
Dysmorphic features					
Relative macrocephaly	N/A	N/A	+	N/A	N/A
Large anterior fontanel	N/A	N/A	+	N/A	N/A
Short neck	N/A	N/A	+	N/A	N/A
Triangular face	N/A	N/A	+	N/A	N/A
Short nose	N/A	N/A	N/A	N/A	N/A
Prominent chin	N/A	N/A	N/A	N/A	N/A
Microretrognathia	N/A	N/A	+	N/A	N/A
Blue sclera	-	-	+	-	-
Shortened of long bones	-	-	+	+	+
Pectus deformity	N/A	N/A	N/A	Pectus carinatum	-
Narrow chest	N/A	N/A	N/A	-	-
Joint hypermobility	N/A	N/A	N/A	-	-
Kyphoscoliosi/ scoliosis	N/A	N/A	+	-	-
Short stature	+	+	N/A	+	-
Hearing loss	-	-	+	-	-

Radiologic featues					
Wormian bones	-	-	+	N/A	N/A
Thin ribs	+	N/A	+	N/A	N/A
Platyspondyly	+	N/A	+	N/A	N/A
Bowing of the long bones	+	-	+	+	+
Coxa valga deformity	+	+	-	N/A	N/A
Generalized osteopenia	+	+	+	+	+
Orodental features	DI (-)	DI (-)	DI (+)	DI (-)	DI (-)
ID/DD	N/A	N/A	+	-	-
Treatment (duration)	Pamidronate 5 to 11 years/zolandronate from 13 years of age	Pamidronate 3 months to 5 years of age /zoledronate from 5 years o age	Pamidronate 38 months	N/A	N/A
BMD Z score before treatment	N/A	N/A	N/A	N/A	N/A
BMD Z score after treatment	N/A	N/A	N/A	N/A	N/A
Decreased of fracture numbers after treatment	+	N/A	+	N/A	N/A
Other comorbidities	Basilar invagination (decompression surgery performed, requring surgical intervention for long bone fractures	Requring surgical intervention for long bone fractures	Requring surgical intervention for long bone fractures, Deceased at age 4.5 years	-	-

Abbreviations: DD: developmental delay, DI: dentinogenesis imperfecta, ID: intellectual disability, MV: mechanical ventilation, MI: mitral insufficiency, MVP: mitral valve prolapse, N: normal, NICU: neonatal intensive care unit, N/A: not available, OI: osteogenesis imperfecta

Table 2. Reported *SERPINH1* Variants: Genotype–Phenotype Correlation

Reference	HSP47 variant *(inheritance)*	Effect on HSP47 Protein	Collagen Biochemical Findings	OI Phenotype Severity

Christiansen *et al.* 2010	*p.L78P (biallelic)*	Unstable; protein degradation via proteasome (null-like)	Misfolded collagen (protease-sensitive; Golgi accumulation); normal posttranslational modification, Rapid ER–Golgi transport of type I procollagen trimers with mildly prolonged ER–extracellular transit	Severe (infantile OI, deforming)
Duran *et al.* 2015	*p.M237T (biallelic)*	Unstable mutant protein; ~50% reduced HSP47 level; ER mislocalization; reciprocal reduction in HSP47 and FKBP65; decreased FKBP65 expression with aberrant localization	Normal collagen folding, normal posttranslational modification, abnormal staining pattern, and massive accumulation in vacuolar-like compartments in the ER	Moderately severe (childhood-onset fractures)
Marshall *et al.* 2016	*p.E113Vfs*8* *(biallelic)*	Frameshift; nonsense-mediated mRNA decay, expected no functional HSP47 (null)	Collagen molecules are expected to display greater structural irregularity and reduced stability	Neonatal lethal OI (perinatal severe)
Essawi *et al.* 2017	*p.E105_H108del (biallelic)*	In-frame deletion in N-terminal domain, likely destabilizes protein (partial function)	Not reported	Moderate (bone fragility, non-lethal)
Song *et al.* 2018	*p.L50R + p.R405H (compound heterozygous)*	Likely alteration in HSP47 function (two missense in trans)	Procollagen misfolding	Moderate (recurrent fractures, deformities in childhood)
Schwarze *et al.* 2019	*p.D412** + upstream deletion of *SERPINH1 (compound heterozygous)*	ER anchor domain is required for protein stability /Partial HSP47 expression (some functional protein present)	Increased trypsin/chymotrypsin sensitivity of type I collagen, normal posttranslational modification	Moderate (siblings with milder deforming OI)
Syx *et al.* 2021	*p.R222S (biallelic)*	Stable levels, but loss of collagen-binding affinity	Overmodified type I procollagen (increased hydroxylation/glycosylation) due to compensatory chaperone binding	Severe (perinatal OI; early lethal)

Aliyeva et al. 2024	*p.E212A (biallelic)*	Alters charged region of collagen-binding interface; predicted to weaken collagen affinity	Not reported	Severe (OI Type III) severe deformities, unable to ambulate
	p.G411S + p.D385N (compound heterozygous)	C-terminal region (near ER-retention RDEL) Minor structural defect; much of HSP47 function retained / Collagen-binding interface (His386 partner) Abolishes Asp–His386 salt bridge; severely impairs pH-dependent collagen binding		Moderate (OI with bone fragility, non-lethal)
Present study	*p.G84R(biallelic)*	Predicted misfolding and ER degradation (by analogy to L78P)	N/A	Moderate to mild (OI with bone fragility, non-lethal)

Abbreviations: ER: endoplasmic reticulum, FKBP65: fk506-binding protein 10; FKBP10, HSP47: heat-shock protein 47 OI: osteogenesis imperfecta,