Case Report

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FKBP10 Variants: Differentiation Between Bruck Syndrome Type 1 And Osteogenesıs Imperfecta Type XI

Gülümay Vural Topaktaş[1], Berna Eroğlu Filibeli[1], Hakan Birinci[1], Özlem Bağ[2], Taha Reşid Özdemir[3], Özgür Kırbıyık[3], Tayfun Çinleti[4], Bumin Nuri Dündar[5]
1İzmir City Hospital, Pediatric Endocrinology Clinic, İzmir, Türkiye
2İzmir City Hospital, Department of Pediatrics, İzmir, Türkiye
3İzmir City Hospital, Genetic Diseases Evaluation Center, İzmir, Türkiye
4İzmir City Hospital, Pediatric Genetic Diseases Department, İzmir, Türkiye
5İzmir Katip Çelebi University Faculty of Medicine, Department of Pediatric Endocrinology, İzmir, Türkiye

What is already known on this topic?
- FKBP10-related osteogenesis imperfecta is a subgroup of osteogenesis imperfecta, and the number of identified patients has increased in recent years with the expansion of genetic studies. These patients typically present with recurrent fractures.

What this study adds?
- Patients with biallelic *FKBP10* variants may initially present with similar features but diverge into BS-1 or OI-XI during follow-up.
- Pterygium and joint contractures in BS-1 may become more apparent or progressive over time, emphasizing the need for long-term monitoring.
- Fractures may persist despite bisphosphonate therapy in BS-1, whereas OI-XI patients generally respond better to treatment.

Abstract
Biallelic *FKBP10* variants cause autosomal recessive osteogenesis imperfecta(OI) type XI (OI-XI) and Bruck syndrome type 1 (BS-1), both characterized by bone fragility. However, BS-1 is additionally marked by joint contractures, leading to diagnostic overlap with OI-XI. To present two *FKBP10*-related cases illustrating the phenotypic continuum and diagnostic challenges between BS-1 and OI-XI. Case 1, a 3.5-month-old male, had multiple fractures, progressive joint contractures, and scoliosis. Genetic testing revealed a novel homozygous *FKBP10* variant, c.603T>A (p.Tyr201Ter), confirming BS-1. Case 2, a 13-day-old male, presented with recurrent fractures but no contractures or pterygium. A pathogenic homozygous *FKBP10* variant, c.890_897dupTGATGGAC (p.Gly300Ter), confirmed OI-XI. Despite bisphosphonate therapy, the BS-1 case continued to experience fractures, whereas the OI-XI patient remained fracture-free with improved bone mineral density. These cases demonstrate that *FKBP10*-related disorders represent a phenotypic continuum rather than distinct entities. Long-term follow-up is crucial, as BS-1 features such as contractures and scoliosis may become more evident or progressive over time. Recognition of evolving phenotypes is essential for accurate diagnosis and management.
Keywords: bone fractures, bruck syndrome, *FKBP10,* joint contractures, osteogenesis imperfecta, pterygium

Gülümay Vural Topaktaş, İzmir City Hospital, Pediatric Endocrinology Clinic, İzmir, Türkiye
gulumayvural3360@gmail.com
0000-0002-2696-0195

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Introduction
Osteogenesis imperfecta (OI) represents a diverse group of hereditary disorders marked by recurrent bone fractures, skeletal deformities, blue sclerae, hearing loss, and short stature (1). These conditions are often linked to heterozygous variants in the *COL1A1* and *COL1A2* genes, which encode the α-1 and α-2 chains of type I collagen (1). Recent genetic studies have identified several recessive forms of OI, with mutations in genes such as *FKBP10* playing a pivotal role in collagen biosynthesis, bone mineralization, and differentiation (2). Specifically, biallelic variants in *FKBP10* are recognized as the underlying cause of autosomal recessive OI type XI (OI-XI) and Bruck Syndrome type 1 (BS-1) (3, 4).
In 1897, Bruck described a male patient with bone fragility and joint contractures, and the syndrome was later named after him (5,6). BS-1 is a genetically and clinically heterogeneous bone fragility disorder with severity ranging from mild to perinatally lethal forms.
Clinically, OI-XI is characterized by frequent bone fractures, skeletal deformities, and short stature. However, classic OI features such as blue sclera, dentinogenesis imperfecta, and hearing loss are uncommon (3, 4, 7, 8). BS-1 exhibits similar clinical manifestations to OI-XI but can be distinguished by the presence of congenital joint contractures and pterygia (4).
This report presents two patients with BS-1 and OI-XI carrying homozygous *FKBP10* variants—one novel, one known—highlighting their overlapping but distinct clinical and genetic features.
Case 1: A 3.5-month-old male infant presented with progressive lower limb swelling. The family reported the recent onset of symptoms, with no prior history of trauma. The patient was born at term via spontaneous vaginal delivery, with a birth weight of 2900 grams. The parents were first-degree cousins, and the paternal lineage exhibited a history of recurrent fractures. However, these fractures occurred following significant trauma. On clinical examination, the patient's anthropometric parameters were as follows: weight 5.8 kg (-0.95 Standard Deviation Score (SDS)), length 61.9 cm (-0.16 SDS) and body mass index (BMI) 15.14 kg/m² (-1.2 SDS). Physical assessment revealed pectus excavatum, right elbow contracture (Figure 1). Bilateral lower limb swelling, tenderness, and superficial ecchymosis were observed. Notably, blue sclerae were absent.
Laboratory analysis revealed the following biochemical parameters: serum calcium 9.9 mg/dL (Normal (N) , 8.9–11.2), phosphorus 6.4 mg/dL (N, 4.8-8.2), alkaline phosphatase 295 U/L (N, 70-350), parathyroid hormone 34.1 ng/mL (N, 15-65), 25-hydroxyvitamin D 32.4 µg/L (N, >30), and a spot urine calcium/creatinine ratio of 0.016 (N, <0.8).
Radiographic evaluation (babygram) identified multiple callus formations on the right humerus, left radius, bilateral femur, and bilateral tibia, suggestive of fractures of varying ages in the absence of documented trauma or falls (Figure 2). Additionally, significant bone demineralization was evident. Dual-energy X-ray absorptiometry (DEXA) performed at 2 years of age showed a corrected bone mineral

density (BMD) lumbar 1-4 (L1-L4) 0,439 gr/cm3 (z-score of +0.84 SDS). As reference data for infants under six months are limited, the result was cautiously interpreted as indicating bone mineralization appropriate for age. The measurement was performed using a Hologic Discovery system and adjusted for age, sex, and body size. Since available pediatric DEXA reference databases include children older than five years, this finding was considered descriptive rather than comparative (9,10).
Genetic analysis revealed a homozygous c.603T>A (p.Tyr201Ter) variant in the *FKBP10* gene, which had not been previously reported in the literature. It was evaluated as likely pathogenic/pathogenic according to American College of Medical Genetics and Genomics (ACMG) criteria (11). Segregation analysis confirmed that both parents were heterozygous carriers of the variant (Figure 3).
Case 2: A 13-day-old male neonate presented with swelling of the left upper extremity. There was no reported history of trauma. The patient was delivered at term via cesarean section, with a birth weight of 3300 grams. The parents were first-degree cousins, and there was no documented family history of recurrent fractures.
On physical examination, the patient's anthropometric parameters were: weight 4 kg (-0.43 SDS), length 55.5 cm (0.74 SDS). Blue sclerae were absent. Clinical assessment revealed swelling and tenderness in the left upper arm and right forearm, with superficial ecchymosis. Laboratory investigations yielded the following biochemical values: complete blood count within normal limits, calcium 10.1 mg/dL (N, 8-11.3), phosphorus 5.9 mg/dL (N, 4.8–8.2), alkaline phosphatase 464 U/L (N, 60–320), parathyroid hormone 18.5 ng/mL (N, 15–65), 25-hydroxyvitamin D 59.9 µg/L (N, >30), and a spot urine calcium/creatinine ratio of 0.016 (N,<0.8).
Radiographic assessment (babygram) revealed multiple fractures involving the right and left humerus, as well as the right ulna, with bilateral callus formation indicative of prior fractures in the thoracic ribs (Figure 4). Additionally, a new fracture was identified in the right eighth posterior rib. Given the suspicion of OI, genetic analysis was conducted, which identified a homozygous pathogenic variant, c.890_897dupTGATGGAC (p.Gly300Ter) (Exon 5), in the *FKBP10* gene. Segregation analysis confirmed heterozygosity for the same variant in both parents (Figure 5).

Materials and Methods

Genetic Analysis

For molecular genetic evaluation, all cases underwent next-generation sequencing (NGS) analysis. In Case 1, molecular analysis was performed using the *Short Stature Panel* (Celemics, Inc., Seoul, Korea), which covers the following 126 genes: *ADAMTS10, ADAMTS2, ADAMTSL4,AGPS, ALPL, ARSE, ATP6V0A2, ATP7A, ATRX, B3GALT6, B4GALT7, BGN, BLM, BRAF, CBL,CBS,CDC6, CDT1,CHST14,COG1,COL10A1,COL11A1, COL1A1, COL1A2, COL2A1, COL3A1, COL4A4, COL5A1, COL5A2, COL9A1, COL9A2, COL9A3, COMP, CREBBP,CRTAP,CTSK,FBLN5,FBN1 FBN2, FERMT1, FGD1, FGF23, FGFR1, FGFR2, FGFR3, FKBP10, FLNA, FLNB, FOXE3, FREM2, GH1, GHR, GHRHR, GLI2,GLI3, GNAS, GNPAT,GRM1, HESX1, HPSE2, HRAS,CUL7,HSPG2, IFITM5, IFT80, IGF1, IGF1R, IL12RB2,INPPL1,KCNJ2,KCNJ8,KDM6A,KMT2D,KRAS,L2HGDH,LAMA3,LBRSBDS,PYCR1,RAF1,RIN2,RIT1,RMRP,ROR2,RPS6KA3,RUNX2,SERPIND1,SERPINH1,SHOC2,SKI,SLC12A6,SLC26A2,SLC2A10,SLC34A3,SLC35D1,SLC39A13,SMAD3,SMARCAL1,SMC1A,SMC3,SMS,SOS1,SOS2,SOX3,SOX6,SOX9,SPRED1,SRCAP,SRY,SUMF1,TDRD7,TGFB1,TGFB2,TGFB3,TGFBR1,TGFBR2,THRB,TRIM37,TRIP11,TRPS1,TRPV4, TTC21B,VCAN,WDR19, WDR35, WNK1, and WRN.* Genomic DNA was obtained from peripheral blood samples for gene sequencing using an NGS-based Target Capture Panel (Short Stature Panel by Celemics, Inc., Seoul, Korea). Target capture NGS was performed using the MiSeq Reagent Nano Kit v3 on the Illumina MiSeq NGS System (Illumina, Inc., San Diego, CA, USA). The resulting FASTQ sequencing files were imported into the "SEQ" variant analysis software (Genomize, Istanbul, Turkey). Pathogenicity assessment of the detected variants was performed according to the ACMG (American College of Medical Genetics) guideline. In Case 2, genomic DNA was isolated from peripheral blood, and sequencing of the *COL1A1, COL1A2,* and *FKBP10* genes was performed using an NGS-based *Skeletal Dysplasia Panel*.

Follow-up

Case 1: The patient was found to carry a homozygous *FKBP10* variant [ENST00000321562.4; c.603T>A (p.Tyr201Ter)], which has not been previously reported in population databases such as ExAC or 1000 Genomes, nor in variant databases such as HGMD and ClinVar. As the clinical features of this case were consistent with the disease phenotype (PP4), the variant was absent from the population (PM2), and it introduced a premature stop codon leading to loss of function (PVS1), it was classified as pathogenic. Since a skeletal dysplasia panel was not available at that time, the short stature panel was utilized for molecular analysis.
The patient was subsequently commenced on intravenous pamidronate therapy at a dose of 0.5 mg/kg/day for three consecutive days, administered every three months. At the most recent follow-up, the patient was 3 years and 11 months old and had sustained a fracture of the left tibia despite ongoing pamidronate therapy. Throughout the treatment period, approximately ten fractures occurred in different anatomical locations. At the latest clinical evaluation, the patient's anthropometric measurements were as follows: weight 12.8 kg (−1.54 SDS), height 93 cm (−1.51 SDS), and BMI 14.8 kg/m² (−0.45 SDS). The patient exhibited a stepping gait, and although the frequency of fractures had decreased with treatment, they persisted. The presence of pterygium, joint contractures, marked scoliosis, pectus excavatum, and a suboptimal therapeutic response led to the diagnosis of BS-1 (Figure 1). When compared with the previous measurement, the most recent L1–L4 BMD value of 0.58 g/cm² demonstrated a progressive improvement in bone mineralization, rather than an age-adjusted comparison; thus, the pamidronate regimen was maintained without modification. The patient continued to receive intravenous pamidronate at a dose of 0.5 mg/kg/day for three consecutive days every three months, along with ongoing physical rehabilitation and calcium–vitamin D supplementation.
Case 2: The patient, whose genetic analysis revealed a homozygous pathogenic variant in the *FKBP10* gene c.890_897dupTGATGGAC (p.Gly300Ter) (Exon 5) previously reported as pathogenic/likely pathogenic in the ClinVar database (ClinVar ID: 631496), was diagnosed with osteogenesis imperfecta type XI (OI-XI). Following the molecular confirmation, the patient began intravenous pamidronate therapy at a dose of 0.5 mg/kg/day for three consecutive days, administered every three months. To date, four treatment cycles have been completed without the occurrence of new fractures. No joint contractures or pterygium have been observed since diagnosis or at the most recent clinical evaluation. Clinical follow-up continues under the confirmed diagnosis of OI-XI. At the latest assessment, at 1 year and 2 months of age, anthropometric measurements were as follows: weight 8.7 kg (−1.77 SDS), length 74 cm (−1.78 SDS), and BMI 15.01 kg/m² (−1.58 SDS). (Table 1 summarizes the present *FKBP10*-related cases compared with previously reported BS-1 and OI-XI cases.)
Written parental consent was obtained for publication.

Discussion

The two cases—one with BS-1 and the other with OI-XI—shared FKBP10 mutations and overlapping early features such as limb swelling, tenderness, and ecchymosis in infancy without trauma. Both had normal biochemical parameters and lacked blue sclerae, dentinogenesis imperfecta, and hearing loss. These similarities highlight the diagnostic challenge of differentiating BS-1 from OI-XI during early infancy (3,4,12,13). The phenotypic heterogeneity of *FKBP10* mutations is well recognized. Alanay et al. (3) and Shaheen et al. (4) showed that these variants can cause either OI-XI or BS-1, with overlapping features such as pterygium and joint contractures. Intra-familial variability has also been described, where siblings with identical mutations present distinct phenotypes—one with BS-1 and another with OI-XI (12). This variability highlights the complexity of genotype–phenotype correlations, supporting a phenotypic continuum rather than separate entities.
Although both OI-XI and BS-1 result from *FKBP10* mutations and exhibit considerable clinical overlap, the timing of fracture onset may differ. While OI can manifest prenatally, intrauterine fractures in OI-XI are rarely documented. In contrast, BS-1 is more commonly

associated with fracture onset later in infancy or early childhood (4, 7, 12, 13). However, as observed in our BS-1 case and previously reported by Alanay et al. (3), fractures may also occur during the early postnatal period, suggesting that this temporal distinction is not absolute (14). These findings further highlight that longitudinal follow-up is essential for delineating the evolving phenotype, particularly for features such as pterygium and contractures that may emerge or progress over time.

Patients with *FKBP10* mutations typically develop recurrent fractures, severe long bone deformities, and progressive kyphoscoliosis. A distinguishing feature of BS-1 is the presence of congenital contractures, particularly affecting the knees, elbows, and ankles, though the onset and severity vary considerably between individuals (4, 8, 12, 13). Such variability reflects collagen cross-linking defects from *FKBP10* loss-of-function mutations. Many affected individuals develop severe disability and lose independent ambulation early (4,7). Consistent with prior reports, our BS-1 case showed progressive contractures and scoliosis requiring neurosurgical and rehabilitative care, while the OI-XI patient maintained normal mobility and motor development (7,8,12,15). These findings highlight the broad phenotypic spectrum of *FKBP10*-related bone fragility and the importance of early physical therapy.

In a study by Ulker et al. (12) analyzing 19 patients with BS-1 and OI-XI, fracture frequency and annual fracture rates were significantly higher in OI-XI compared to BS-1. While bisphosphonate therapy effectively reduced fractures in OI-XI patients, it had a limited impact in BS-1. Despite increases in BMD and reduced bone pain, BS-1 patients did not achieve independent ambulation, reflecting poor overall prognosis. Our BS-1 case similarly experienced persistent fractures despite improved BMD, whereas the OI-XI patient remained fracture-free following treatment, aligning with these observations. These observations support prior evidence that bisphosphonates improve BMD but do not fully prevent fractures in *FKBP10*-related BS-1 (3, 12, 14). Despite regular pamidronate therapy and improved bone mineral density, the patient experienced approximately ten fractures at different skeletal sites during follow-up, consistent with previous reports showing that bisphosphonate treatment increases bone density but does not completely prevent fractures in *FKBP10*-related BS-1(3,4,16). Cognitive and auditory functions are usually preserved in *FKBP10*-related disorders, as observed in both cases. Craniofacial dysmorphism, including triangular facial shape and brachycephaly, along with progressive kyphoscoliosis, has been reported and may aid in distinguishing BS-1 from other fragility disorders such as OI-III and arthrogryposis multiplex congenita (14,15). Overall, our findings reinforce that *FKBP10*-related bone fragility disorders form a phenotypic continuum rather than discrete entities, underscoring the importance of multidisciplinary long-term follow-up to monitor skeletal deformities, motor function, and therapeutic response.

Conclusion

This study underscores the diagnostic challenge of distinguishing BS-1 from OI-XI. Over time, pterygium and joint contractures become more evident in BS-1 but are typically absent in OI-XI. Although both share *FKBP10* variants, fractures may persist in BS-1 despite bisphosphonate therapy, whereas OI-XI generally shows a better response. These observations highlight the need for careful clinical evaluation and long-term follow-up in FKBP10-related bone fragility disorders.

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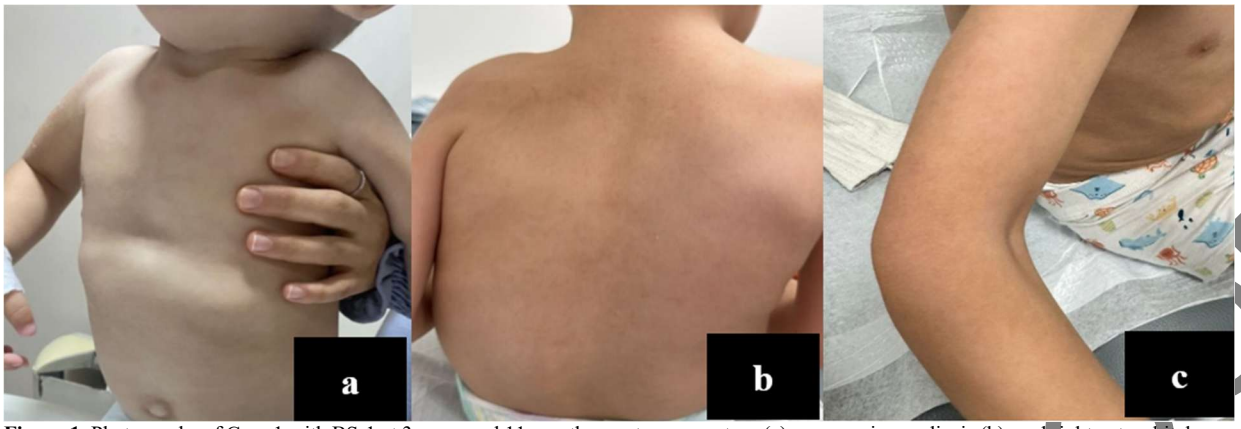

Figure 1. Photographs of Case 1 with BS-1 at 3 years and 11 months: pectus excavatum (a), progressive scoliosis (b), and right antecubital pterygium (c).

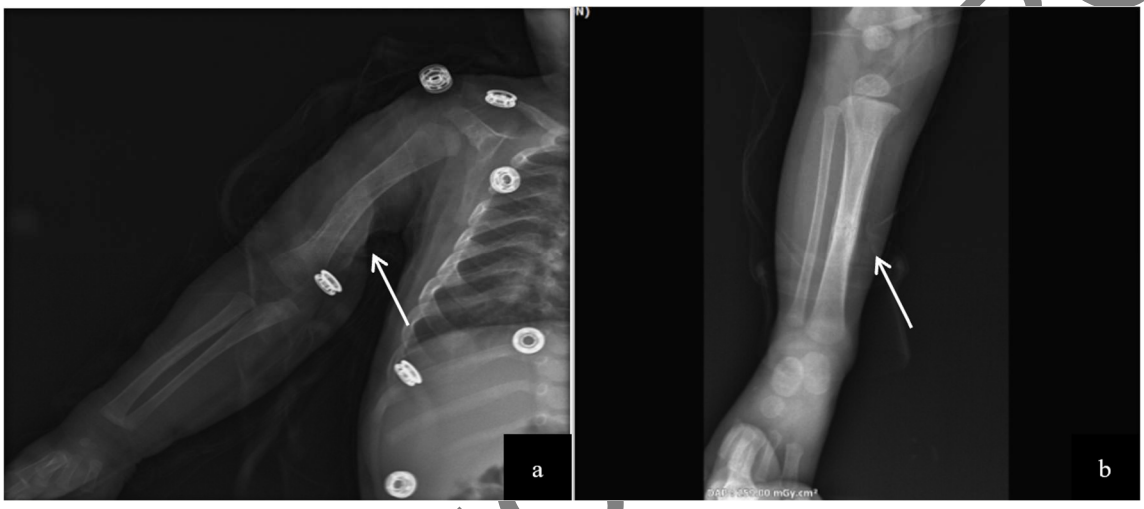

Figure 2. Babygram of Case 1 diagnosed with BS-1. Arrows indicate callus formations on the right humerus (a) and left radius (b).

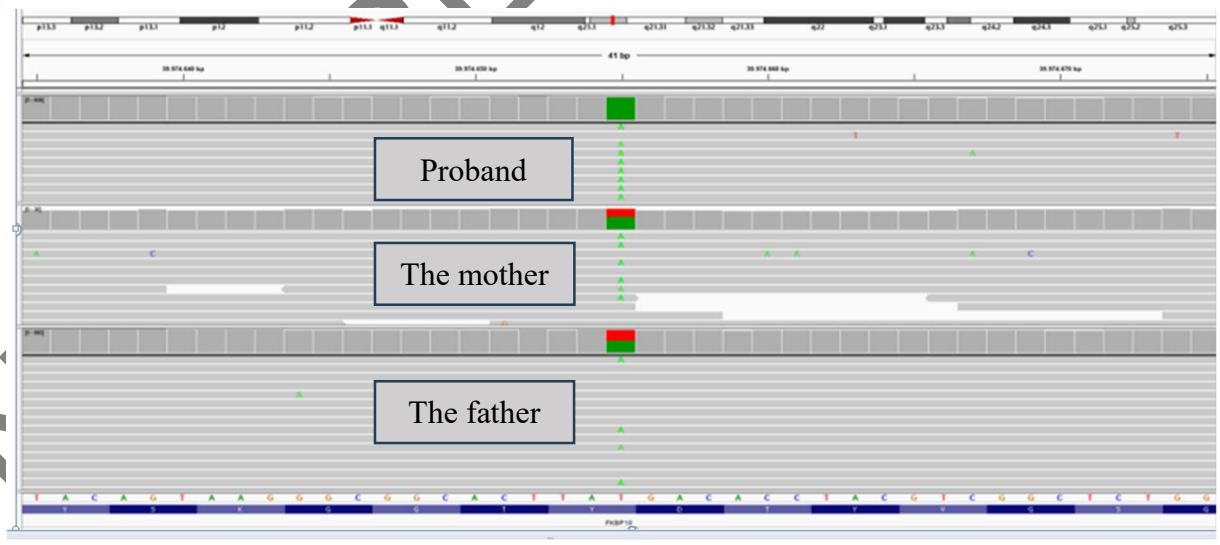

Figure 3. IGV images of Case 1 showing the homozygous *FKBP10* c.603T>A (p.Tyr201Ter) variant in the proband, with both parents being heterozygous carriers.

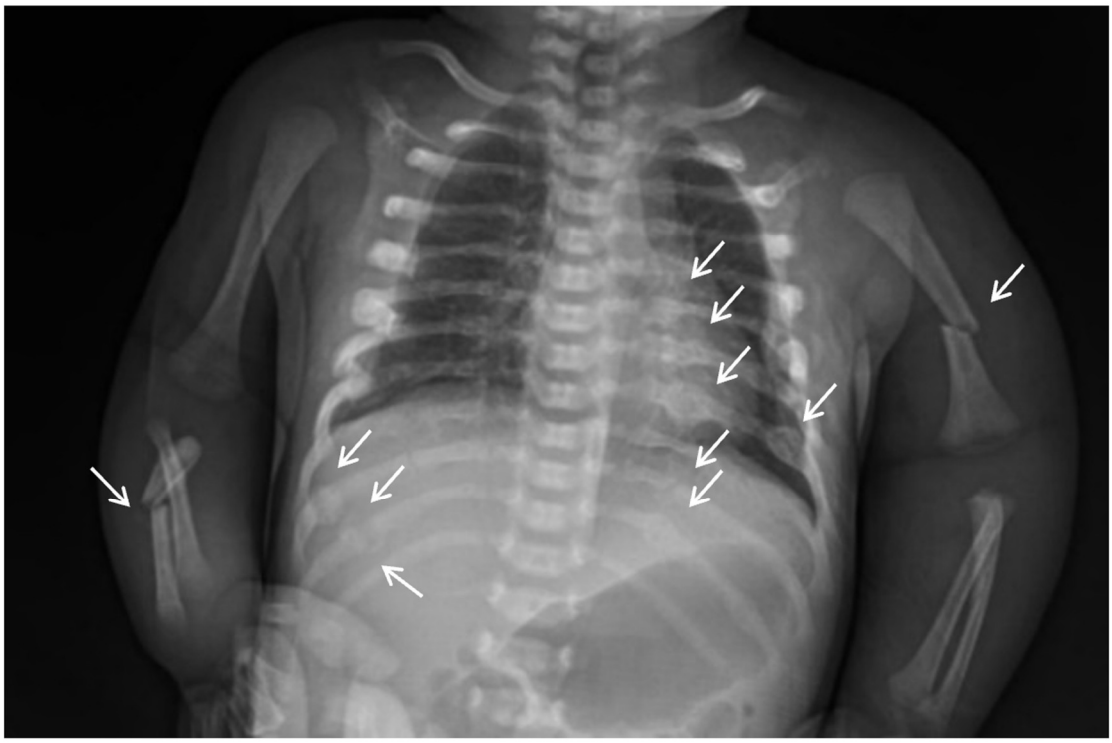

Figure 4. Babygram of Case 2 diagnosed with OI-XI, arrows indicate fractures and callus formations

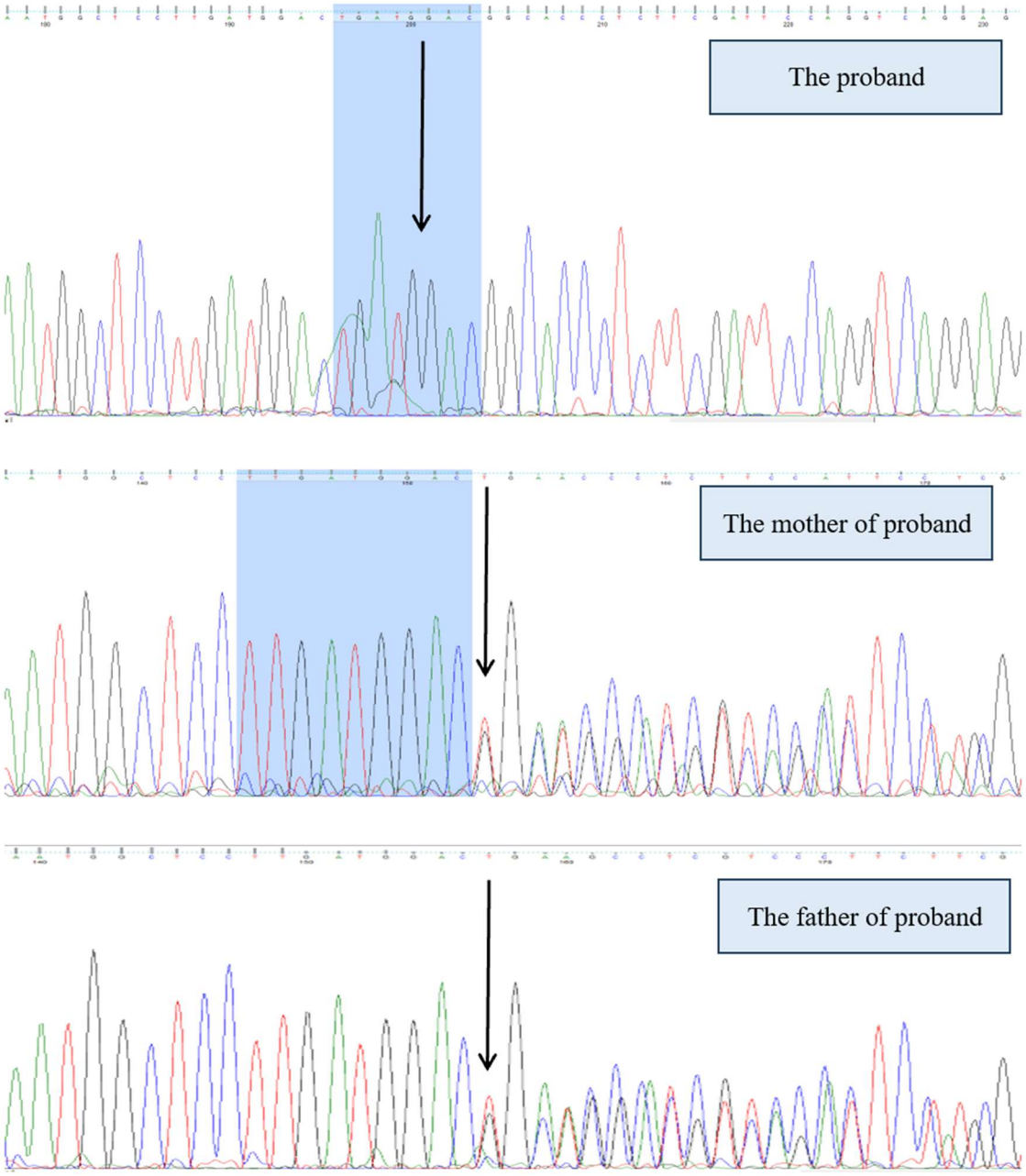

Figure 5. Electropherograms of Case 2 showing the homozygous *FKBP10* c.890_897dup (p.Gly300Ter) variant in the proband, with both parents being heterozygous carriers.

Table 1. Comparison of the present *FKBP10*-related cases with reported BS-1 and OI-XI cases

Parameter	**Case 1 (BS-1)**	**Case 2 (OI-XI)**	**Reported BS-1 (Alanay et al.,[3]; Shaheen et al., [13]; Ülker et al., [12])**	**Reported OI-XI (Alanay et al., [3]; Shaheen et al., [13]; Essawi et al., [8])**
Sex	Male	Male	M/F	M/F
Age at diagnosis	3.5 months	13 days	Infancy – early childhood	Neonatal – childhood
Consanguinity	Present (first-degree cousins)	Present (first-degree cousins)	Common in reported families	Common in reported families
Genetic variant	*FKBP10* c.603T>A (p.Tyr201Ter), homozygous (novel)	*FKBP10* c.890_897dupTGATGGAC (p.Gly300Ter), homozygous (reported)	Various homozygous or compound heterozygous loss-of-function variants	Similar biallelic loss-of-function variants
Main clinical findings at presentation	Limb swelling, tenderness, ecchymosis, pectus	Limb swelling, tenderness,	Congenital contractures, joint pterygia, bone fragility	Recurrent fractures, short stature, skeletal deformities

	excavatum, right elbow contracture	ecchymosis		
Blue sclera / Dentinogenesis imperfecta / Hearing loss	Absent	Absent	Usually absent	Occasionally present
Joint contractures	Present (elbow, wrist, knee) progressive	Absent	Present in most patients and progressive	Absent or mild
Pterygium	Appeared later (antecubital region)	Absent	Frequently present (congenital or progressive)	Absent
Kyphoscoliosis	Progressive	Absent	Common and progressive	Variable severity
BMD (L1-L4) (Before treatment)	0,439 gr/cm3 (at 2 years of age)	Not performed	Reduced BMD (< −2 SDS)	Reduced BMD (< −2 SDS)
BMD (L1-L4) (After treatment)	0.58 gr/cm3	Not performed	Improved BMD with bisphosphonates, but fractures may persist	Improved BMD and reduced fracture frequency
Treatment	IV pamidronate (0.5 mg/kg/day × 3 days every 3 months) + Ca/Vit D + rehabilitation	IV pamidronate (0.5 mg/kg/day × 3 days every 3 months) + Ca/Vit D	IV bisphosphonate therapy long-term	IV bisphosphonate therapy long-term
Response to treatment	~10 fractures despite improved BMD; non-ambulatory	No new fractures; normal motor development	Partial response; fractures may continue despite BMD gain (Ülker et al.)	Favorable response with increased BMD and reduced fractures
Cognitive / Auditory function	Normal	Normal	Preserved	Preserved
Radiographic findings	Multiple callus formations, osteopenia, long bone deformities	Multiple callus formation	Severe osteopenia, long bone deformity, wormian bones	Osteopenia, vertebral compression fractures
Prognosis	Severe skeletal deformity, poor functional outcome	Milder phenotype, favorable outcome	Limited mobility, progressive contractures	Ambulatory, variable severity
BS1: Bruck syndrome type 1, OI-XI: osteogenesis imperfecta(OI) type XI, M/F: Male/Female, BMD (L1-L4) :Bone mineral density (measured at lumbar vertebrae L1–L4), IV: Intravenous				