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Case Report

A Rare Cause of Sacral Insufficiency Fracture in Adolescence: Autosomal Dominant Hypophosphatemic Rickets due to *Fgf23* de novo P.Arg176trp Variant

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What is already known on this topic?
Autosomal dominant hypophosphatemic rickets (ADHR) is a rare, hereditary disorder caused by gain-of-function mutations in the *FGF23* gene. ADHR shows variable clinical presentation, with symptoms such as rickets in childhood or bone pain and fractures in adolescence or adulthood. Management typically mirrors that of X-linked hypophosphatemia (XLHR), including phosphate and active vitamin D supplementation, though standardized ADHR-specific guidelines are lacking.

What this study adds?
This is the first reported case of ADHR presenting with bilateral sacral insufficiency fractures in adolescence, without prior trauma. The identified c.526C>T (p.Arg176Trp) variant was de novo, and unlike some previously reported familial cases, spontaneous remission has not been observed. Despite normal bone mineral density, the patient experienced pathological fractures, highlighting a potential dissociation between densitometry results and fracture risk in ADHR. The case emphasizes the need for heightened clinical suspicion and long-term follow-up in adolescents with unexplained fractures, even without typical rickets findings. The highlighting the need for a comprehensive clinical assessment beyond BMD measurements in adolescents with suspected bone disease.

ABSTRACT
Autosomal dominant hypophosphatemic rickets (ADHR) is a rare metabolic bone disease with variable clinical presentation, caused by pathogenic variants in the *FGF23* gene. The disease typically manifests in childhood with growth retardation and rickets symptoms, but may also be diagnosed in adolescence or adulthood with atypical symptoms. We present a 14-year and 5-month-old female patient who presented with bilateral sacral insufficiency fractures following a subtle onset without a history of trauma. Diagnostic tests revealed findings consistent with hypophosphatemic rickets and a de novo heterozygous c.526C>T (p.Arg176Trp) variant in the *FGF23* gene, leading to a diagnosis of ADHR. The patient had no significant history of rickets during childhood. She had lived for approximately one year with complaints of progressive pain in the lower lumbar region, which worsened with walking and sitting, without receiving a diagnosis. Bilateral sacroiliac insufficiency fractures and hypophosphatemia were detected, and genetic analysis was performed. The patient underwent bilateral sacroiliac fracture fixation by pediatric orthopedics, and phosphate and active vitamin D (calcitriol) therapy was initiated by pediatric endocrinology. Clinical symptoms improved significantly during follow-up. Due to its genetic and clinical heterogeneity, autosomal dominant hypophosphatemic rickets (ADHR) is a disease that can cause delays in diagnosis. The number of cases reported in the literature associated with this variant is limited, and this is, to the best of our knowledge, the first report of an adolescent with ADHR diagnosed with bilateral sacral insufficiency fractures. This case is important for raising awareness of ADHR and highlighting the broad clinical spectrum of the disease. Sharing the diagnostic and treatment processes will be helpful for clinicians encountering this rare disease.
Keywords: Adolescent, bone disease, autosomal dominant hypophosphatemic rickets, fibroblast growth factor 23, hypophosphatemia, sacral insufficiency fracture

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INTRODUCTION

Hypophosphatemic rickets is a rare metabolic bone disease that develops due to renal phosphate loss. One of the primary factors involved in the pathogenesis of the disease is fibroblast growth factor 23 (*FGF23). FGF23* is a hormone secreted by osteoblasts and osteocytes that reduces phosphate reabsorption in renal proximal tubules by its phosphaturic effect and also suppresses the production of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. This hormone is regulated in response to serum phosphate levels and increases, particularly in conditions of oral phosphate intake or hyperphosphatemia, leading to increased phosphate excretion in the urine and causing hypophosphatemia (1,2). Among hereditary hypophosphatemic diseases related to *FGF23*, ADHR occupies a special place, as it is caused by pathogenic variants in the FGF23 gene (3). ADHR occurs in approximately 2% of all hypophosphatemic rickets cases and can pose diagnostic challenges due to its clinical and laboratory findings being similar to those of X-linked hypophosphatemic rickets (XLHR) (4). The most frequently detected genetic changes in ADHR cases are missense mutations in the arginine residues at codons 176 or 179 of the *FGF23* gene (R176Q, R176W, R179Q, R179W) (including the variant identified in our patient). These mutations lead to a gain-of-function effect by increasing the resistance of the *FGF23* protein to proteolytic degradation, playing a critical role in the pathogenesis of the disease.
The clinical course in ADHR is quite heterogeneous; the disease's penetrance is usually incomplete, and symptoms can appear at different stages, ranging from early childhood to adulthood. In early ages, patients commonly present with growth retardation, limb bowing, and rickets symptoms, while in later ages, musculoskeletal pain, osteomalacia, and pathological fractures become more prominent. Therefore, ADHR can present with varying clinical pictures depending on age and may lead to delays in diagnosis (5,6).

Bilateral sacral insufficiency fractures are uncommon but clinically important injuries, often seen in patients with osteoporosis or metabolic bone diseases. This article presents an adolescent female patient diagnosed with bilateral sacral insufficiency fractures without a history of trauma and exhibiting a slow, insidious onset. Genetic analysis revealed a pathogenic variant in the *FGF23* gene, leading to the diagnosis of ADHR. Given the rarity of ADHR cases diagnosed with sacral insufficiency fractures in the literature, this case is important both for raising clinical awareness and contributing to the diagnostic process.

CASE PRESENTATION

BRIEF HISTORY OF THE CASE:

A 14-year and 5-month-old female patient was referred from the rheumatology clinic to the pediatric endocrinology department due to a sacral fracture that developed in the absence of trauma. The patient had no pathological history during the perinatal or early childhood period. The patient had no history of long-term corticosteroid use. It was learned that her hip pain began approximately one year prior, gradually intensified over time, and eventually led to immobility. The patient had previously been evaluated in orthopedic and rheumatology clinics, and radiological imaging revealed a sacral fracture (Figures 1-3). Initial laboratory evaluation showed hypophosphatemia and elevated alkaline phosphatase levels. The tubular reabsorption of phosphate (TRP) was calculated at 84.8%. This value is low. The patient's detailed laboratory findings are presented in the table. In addition, malignancy screening (due to fracture in absence of trauma)—including peripheral blood smear, bone marrow aspiration, and multiple myeloma panel—was unremarkable. No rachitic changes were observed in the metaphyses on knee radiography. Bone mineral density assessment revealed a Z-score of –1.21 SDS. The BMD measurement referenced was indeed from the lumbar spine (L1–L4) (7). A lateral radiograph of the thoracolumbar spine was obtained and showed no evidence of vertebral fractures.

RESULTS

On physical examination, the patient's height was 160 cm (–0.17 SDS), weight was 65 kg (+1.43 SDS), and body mass index (BMI) was 25.3 kg/m² (+1.42 SDS). She was assessed to be at Tanner stage 5. The patient reported having regular menstrual cycles. Internal and external hip rotation movements were painful and limited. She was able to mobilize with support, although with significant pain. The patient described maximum pain when transitioning between sitting and standing positions. Interestingly, she reported less discomfort while standing compared to lying down. On examination, bilateral pain and tenderness were noted during sacral provocation tests.

The patient had previously been treated with naproxen sodium, lansoprazole, and an effervescent tablet containing calcium and vitamin D, and had intermittently received vitamin D supplementation. Due to the presence of hypophosphatemia and elevated alkaline phosphatase (ALP), and considering her age and the pathological nature of the fracture, a malignancy workup was initiated. Tubular reabsorption of phosphate (TRP) was 84.8%. Peripheral blood smear, bone marrow aspiration, and multiple myeloma screening revealed no abnormalities. Knee radiographs showed no metaphyseal irregularities. Incidentally, a non-ossifying fibroma (NOF) was detected in the right tibia. Bone mineral density assessment revealed a Z-score of –1.21 SDS for her age.

The patient was started on phosphate replacement therapy at a dose of 25 mg/kg/day and active vitamin D (calcitriol) at a dose of 30 ng/kg/day. Following one month of conventional therapy, sacroplasty was scheduled to address the sacral fracture.

Under general anesthesia and fluoroscopic guidance, bilateral in situ pinning of the S1 level was performed using 6.5 mm fully threaded cannulated screws (Figures 4-5), after one month of conventional therapy.

GENETIC ANALYSIS

Whole exome sequencing analysis of DNA isolated from peripheral blood revealed that the patient carried the c.526C>T variant in the ***FGF23*** gene with an allelic frequency of 63% (rs754201217)(Figure6).

This variant has previously been described in the literature (PMID: 31486862) and is reported as pathogenic in the ClinVar database (ClinVar ID: 1072118) (8).

Not reported in population frequency studies, this variant has been predicted to be deleterious by most *in silico* analyses and has been classified as likely pathogenic according to American College of Medical Genetics and Genomics (ACMG) criteria (PM1, PM2, PM5, PP2, PP5).

In the family history of the patient, it was learned that there were no similar clinical conditions and her parents were not consanguineous. Her mother had a history of three early abortions before and three after the index case. Familial segregation analysis showed that the parents did not carry the c.526C>T(p.Arg176Trp) (NM_001130438.3) variant in *FGF23*. The variant detected in the patient was evaluated as de novo (figure 7).

During follow-up, the patient's clinical status and radiological findings showed marked improvement. Hip and leg pain gradually subsided, and she began walking independently and pain-free. Exercise tolerance increased (Figure 8). Meanwhile, the results of genetic testing were obtained. A heterozygous c.526C>T p.(Arg176Trp) variant (rs754201217) was identified in the ***FGF23*** gene. Since this variant was not detected in either parent, it was considered a de novo mutation. In line with the clinical presentation, the patient was diagnosed with ADHR. The identification of a de novo mutation in our patient is particularly noteworthy, as de novo variants in ADHR are infrequently reported in the literature, highlighting the unique contribution of this case.

By the second postoperative month, independent ambulation had been achieved. During the 4-month follow-up, laboratory parameters were monitored regularly (Table). At the most recent visit, the treatment regimen was updated to phosphate (Sandoz) 1.5 tablets four times daily (45 mg/kg/day) **and** calcitriol 30 ng/kg/day**.** A transient elevation in parathyroid hormone (PTH) levels was observed but normalized over time. Renal ultrasonography showed no evidence of nephrocalcinosis. Family-based genetic screening and pedigree analysis are planned for future studies.

The patient is scheduled for biochemical parameter monitoring every three months and renal ultrasound annually.

DISCUSSION

In this study, a 14-year-old girl with no history of trauma who presented with bilateral sacral insufficiency fractures was diagnosed with ADHR after identification of a heterozygous c.526C>T p.(Arg176Trp) variant in the *FGF23* gene. To the best of our knowledge, this is the first report of an ADHR case diagnosed with bilateral sacral insufficiency fractures in the literature.

ADHR is a rare hereditary form of hypophosphatemic rickets caused by gain-of-function mutations in the *FGF23* gene. The disease exhibits a high degree of clinical heterogeneity. In some patients, rickets, growth retardation, and lower extremity deformities are prominent during childhood, while others present with bone pain, osteomalacia, and pathological fractures in adolescence or adulthood. These clinical differences may be associated with variability in the disease's penetrance.

In the presented case, no signs of rickets were observed during childhood, and the clinical symptoms appeared only in the past year. This is similar to the case reported by Tanaka et al., in which an adolescent was diagnosed with ADHR and a novel variant in the *FGF23* gene. In their case, symptoms spontaneously resolved after a period, and a similar variant was identified in the asymptomatic father (9). In our case, spontaneous remission has not yet been observed, and clinical improvement was achieved through medical treatment. The variant in our patient was identified as de novo.

In a study evaluating 11 ADHR cases by Liu et al., 10 patients presented symptomatically, with significant bone mineral density loss and fractures observed in these individuals (10). Although sacral insufficiency fractures were present in our case, bone mineral densitometry did not show osteoporosis. This highlights the potential for pathological fractures to develop even when bone mineral density remains within normal limits in ADHR cases, which is noteworthy for clinical evaluation. Our case demonstrates a distinct presentation in this regard.

In a case reported by Mameli et al., a 17-month-old girl with clinical and radiological rickets findings was found to have a c.536G>A variant in the third exon of the *FGF23* gene. This variant, located in the R179 region, was suggested to be associated with an earlier onset and more severe phenotype compared to R176 mutations. Spontaneous clinical improvement was observed when the patient reached 6 years and 6 months of age (11). In our case, although the treatment process is still in the early stages, there has been dramatic clinical improvement following medical treatment. Long-term follow-up is planned to assess the possibility of spontaneous remission.

The management of ADHR is primarily based on treatment strategies for X-linked hypophosphatemic rickets (XLHR)**,** due to the limited literature on this rare disease and the absence of specific treatment guidelines for ADHR. The main goal of treatment is to correct hypophosphatemia and support bone mineralization. Oral phosphate supplementation is typically administered in multiple doses per day due to its short half-life, with the recommended dose usually ranging from 40–60 mg/kg/day divided into 3–5 doses (12). Treatment efficacy is monitored based on bone pain, growth rate, alkaline phosphatase levels, and skeletal deformities. The most common complication associated with treatment is secondary hyperparathyroidism (13). Active vitamin D analogs should be dosed according to age and growth rate (20–30 ng/kg/day). The most significant side effect of these agents is nephrocalcinosis, which necessitates regular ultrasonographic screening (12,13).

In the presented case, a transient increase in parathyroid hormone levels was observed during the third month of treatment, which subsequently normalized. Renal ultrasonography findings were normal. Additionally, significant improvement in the bilateral sacral insufficiency fractures was observed after medical treatment and sacroplasty, suggesting that early diagnosis and appropriate treatment can reduce skeletal morbidity associated with ADHR.

Recently, burosumab, a monoclonal antibody that neutralizes the effect of *FGF23*, has been used in the treatment of XLHR, but it has not yet been systematically evaluated in ADHR cases. Therefore, further studies are required to assess its efficacy and safety. To our knowledge, there is currently no published study on its use in ADHR.

CONCLUSION

In this case, a patient presented with bilateral sacral insufficiency fractures in adolescence without a history of trauma, and a pathogenic variant identified in the *FGF23* gene led to the diagnosis of ADHR. The clinical presentation of ADHR can be highly variable, and in some cases, the disease may progress unnoticed during childhood and only become apparent during adolescence or adulthood. Therefore, metabolic bone diseases should always be considered in the differential diagnosis, especially in adolescent and young adult patients presenting with pathological fractures.

The presented case is associated with one of the rarely reported genetic variants in the literature and is among the first cases diagnosed with sacral insufficiency fractures. Increasing clinical awareness is crucial for early diagnosis and for preventing serious complications such as skeletal deformities and fractures through appropriate treatment.

The limited knowledge and experience regarding ADHR may lead to uncertainties in the diagnosis and treatment processes. Therefore, reporting similar cases will contribute to a better understanding of the clinical spectrum of the disease and the development of treatment approaches. Unexplained bone pain, growth retardation, or recurrent fractures seen in childhood and adolescence should particularly raise suspicion for rare phosphate metabolism disorders such as ADHR. Further studies and reports are needed in the future to better understand and treat ADHR, especially in children.

Informed Consent: Additionally, informed consent for the publication of this case report, including the use of clinical details and images, was obtained from the patient's family.

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Table 1: Laboratory parameters of the patient

	Initial	1st m* (surgery time)	2nd m* (1st month postoperative)	3rd m*(2nd month postoperative)	4th m*(3rd month postoperative)	6th m*(5th month postoperative)
Creatinine (mg/dl) (range:0,5-0,9)	0,47	0,5				
Calcium (mg/dl) (range:8,4-10,2)	9,9	8,46	9,8	9,3	9	
Phosphorus (mg/dl) (range:2,5-4,8)	1,59	2,68	1,22	1,68	3,26	2,35
Magnesium (range:1,7-2,2)	1,82	2			1,9	
Alkaline Phosphatase (U/l) (range:50-117)	459	528	520	540	402	
Albumin (g/l) (range:32-45)	47					
Parathyroid hormone (pg/ml) (range:15-65)	19,7	35,4	132	192	56	
25OH vitamin d (ng/ml) (range:30-100)	25					
1,25-dihydroxyvitamin D (pg/ml)(range-20-60)	31,6					
TSH (uIU/ml)** (range:0,5-4,3)	2,1					
fT4 (ng/dl) (range:0,98-1,63)	1,33					
TRP (%)(range:85-95)***	84,8					
TmP/GFR (mmol/l)(range:1,15-1,8)****	1,32					
Serum amyloid A(mg/dl)(range:(<1)	0,29					
Erythrocyte sedimentation rate (mm/h)(range:<15)	11					
C3 (g/l)(range:0,9-1,8)	1,36					
C4 (g/l)(range:0,1-0,4)	0,26					
Brucella Coombs	negative					

*Parameters were tested at the end of specified month, ** Thyroid Stimulating Hormone,
*** Tubular Phosphate Reabsorption, ****Tubular maximum for phosphate reabsorbtion to glomerular filtration rate

1a **1b**

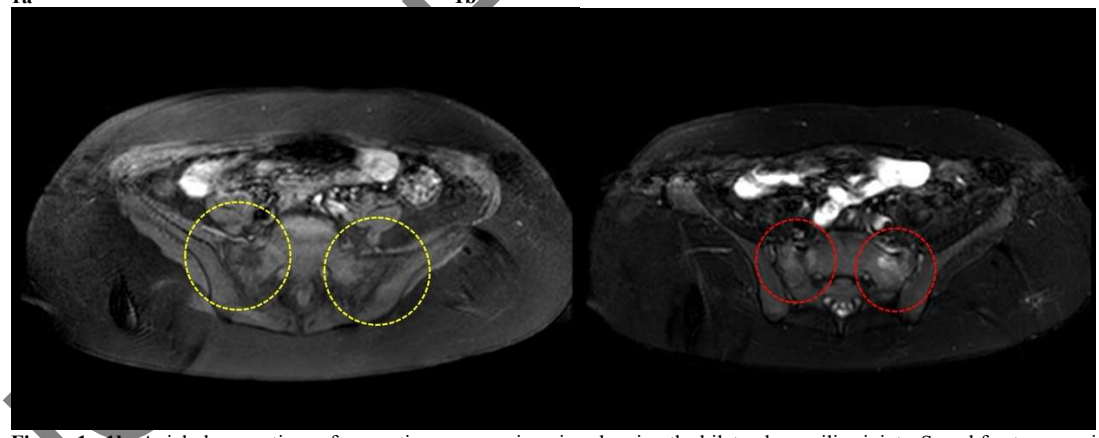


Figure 1a-1b: Axial plane sections of magnetic resonance imaging showing the bilateral sacroiliac joints. Sacral fractures are indicated by yellow and red dashed circles on both sides. T1-weighted (left) and T2-weighted (right) axial MRI images demonstrate hypointense signals (1a) and hyperintense signals (1b) localized to the bilateral sacral ala.

2a 2b

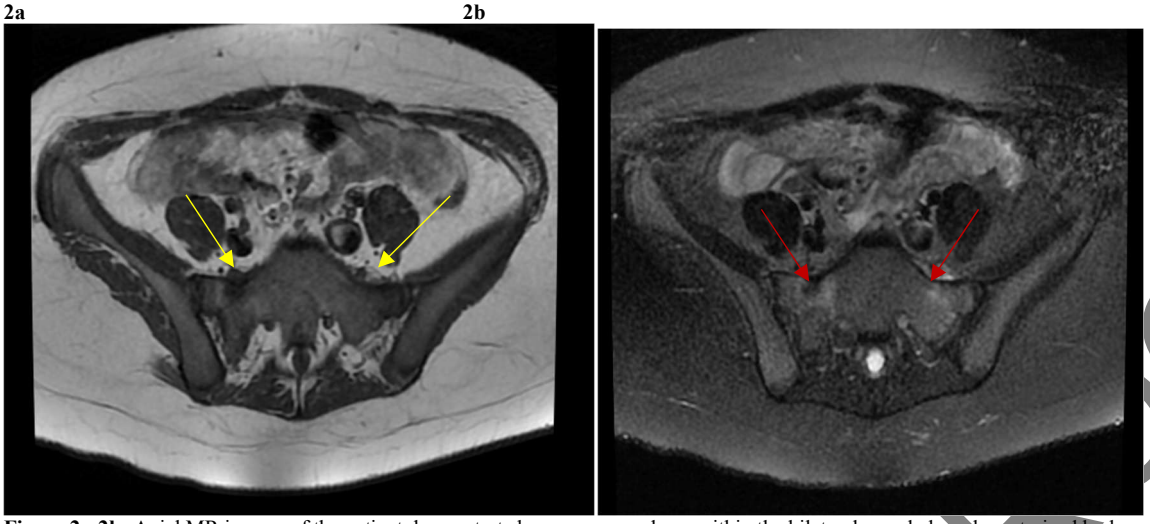
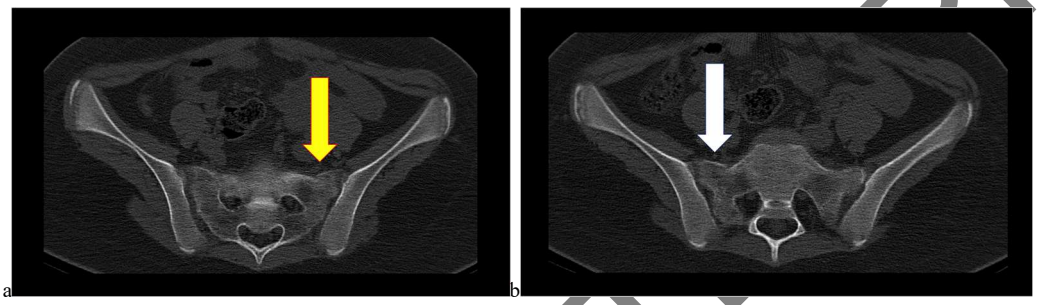


Figure 2a-2b: Axial MR images of the patient demonstrate bone marrow edema within the bilateral sacral alae, characterized by hypointense signals on T1-weighted sequences (yellow arrows, 2a) and hyperintense signals on T2-weighted sequences (red arrows, 2b).



a b

Figure 3a -3b: Axial sections of pelvic computed tomography showing the maximum displacement at the left (yellow arrow) and right (white arrow) sacroiliac joints. This image was obtained at the referral hospital where the authors are currently working.

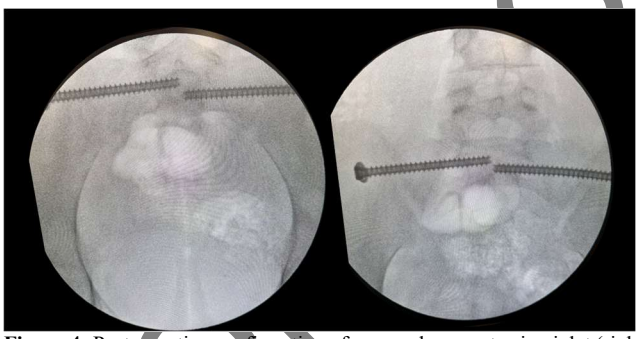


Figure 4: Postoperative confirmation of screw placement using inlet (right) and outlet (left) views.

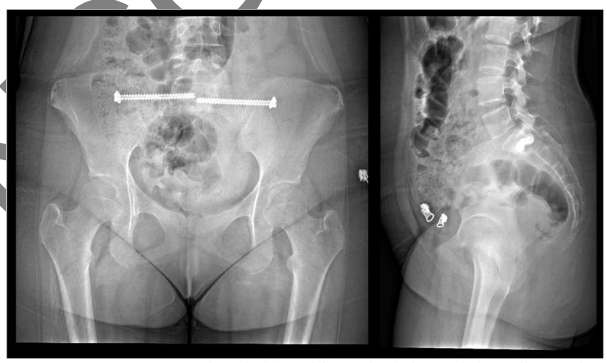


Figure 5: Anteroposterior (left) and lateral (right) pelvic radiographs at postoperative week 3. Note that both screws are located within the S1 vertebral body in the lateral view

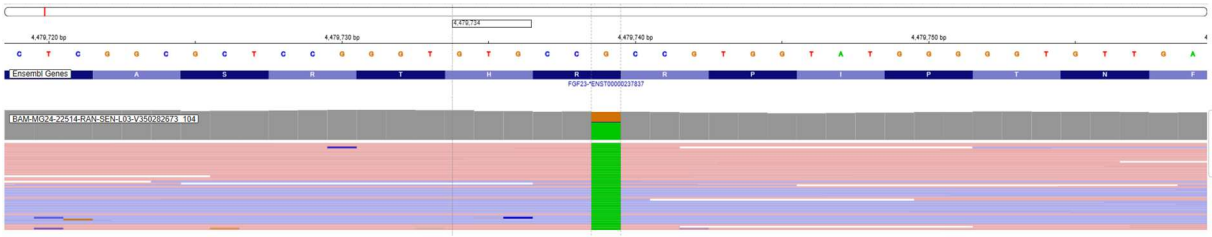


Figure 6. Integrative Genomic Viewer (IGV) image of forward and reverse reads of c.526C>T change detected in *FGF23*.

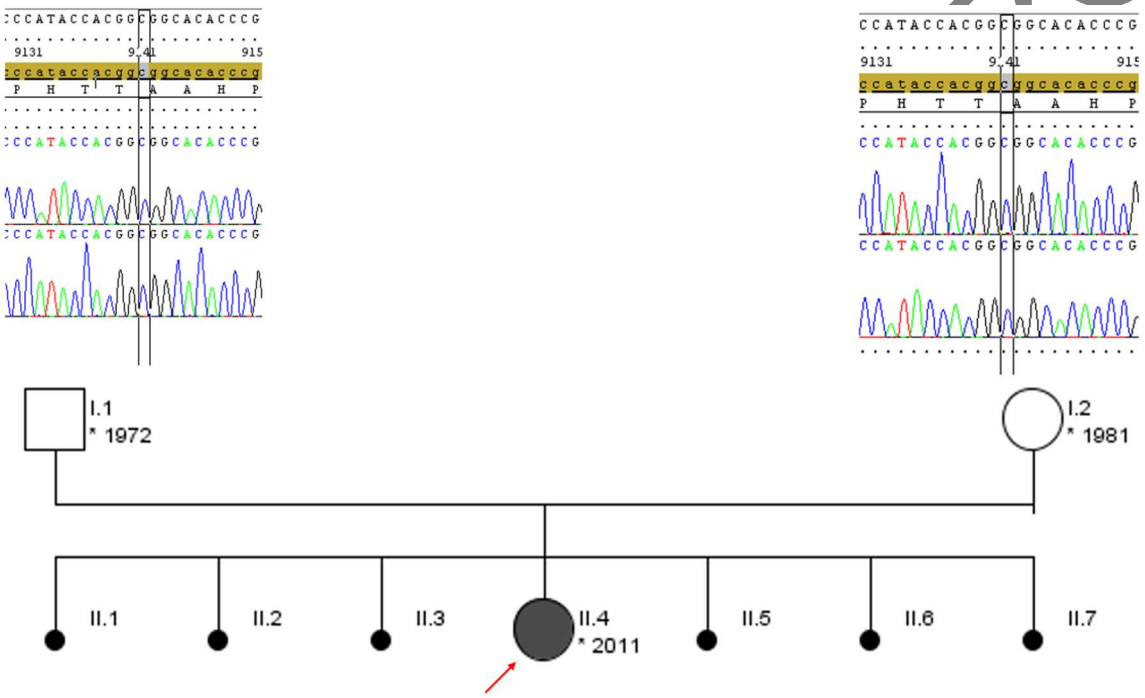


Figure 7. Familial segregation analysis of Sanger sequencing images on pedigrees

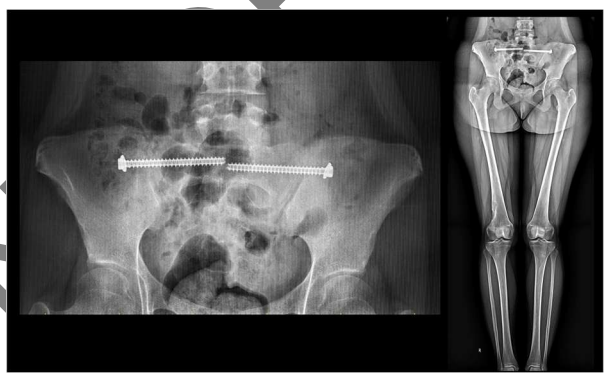


Figure 8: Radiographic images at 6 months postoperatively showing complete healing and proper alignment: pelvic radiograph (left) and standing full-length orthoroentgenogram (right)