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Case report

A novel compound heterozygous variation in the *FKBP10* gene causes Bruck syndrome without congenital contractures: A case report

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ABSTRACT

Background: Bruck syndrome (BS) is an extremely rare autosomal-recessive connective tissue disorder mainly characterized by bone fragility, congenital joint contracture, and spinal deformity. It is also considered as a rare form of osteogenesis imperfecta (OI) due to features of osteopenia and fragility fractures. Its two forms, BS1 and BS2, are caused by pathogenic variations in *FKBP10* and *PLOD2*, respectively.

Objective: We aimed to improve the clinical understanding of BS by presenting a case from China and to identify the genetic variants that led to this case.

Methods: OI was suspected in a Chinese boy with a history of recurrent long bone fractures, lumbar kyphosis, and dentinogenesis imperfecta (DI). Whole-exome sequencing (WES) was performed to identify pathogenic variations. Sanger sequencing was used to confirm the results of the WES. *In silico* analysis was used to predict the pathogenicity of genetic variants.

Results: WES and Sanger sequencing revealed a compound heterozygous variation in the *FKBP10* gene (NM_021939, c.23dupG in exon 1, and c.825dupC in exon 5). Both variants resulted in a frameshift and premature stop codon. Of these two variants, c.23dupG has not been previously reported. The patient's parents were heterozygous carriers of one variant. In addition, zoledronic acid treatment improved the vertebral deformity and bone mineral density (BMD) significantly in this patient.

Conclusions: A novel compound heterozygous variation of *FKBP10*, c.23dupG/c.825dupC, was identified in a patient with moderately severe OI. Based on these findings, the patient was diagnosed with BS1 without congenital joint contractures or OI type XI. This study expands the spectrum of *FKBP10* genetic variants that cause BS and OI.

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1. Introduction

Bruck syndrome (BS) is a rare autosomal-recessive connective tissue disorder characterized by bone fragility and congenital contractures. It is named after German doctor Alfred Bruck, who reported the first case in 1897 [1]. Due to characteristics of osteopenia and fragility fractures, BS is also considered as an extremely rare form of osteogenesis imperfecta (OI) [2,3]. In addition, patients diagnosed with BS often present with pterygia, short stature, progressive scoliosis, limb deformities, Wormian skull bones, and blue/grey sclera [4,5]. A few cases exhibit dentinogenesis imperfecta (DI) [6,7].

According to the causative genetic loci, BS is delineated into two types, Bruck syndrome type 1 (BS1, OMIM 259450) and Bruck syndrome type 2 (BS2, OMIM 609220), which are caused by pathogenic variations in the *FKBP10* and *PLOD2* genes, respectively [6,8,9]. BS1 and BS2 are phenotypically indistinguishable. The *FKBP10* gene (17q21.2) encodes FK506 binding protein 65 (FKBP65), an endoplasmic reticulum resident protein with peptidyl-prolyl-isomerase (PPIase) activity [10,11]. It associates with triple-helical collagen and functions as a chaperone [12]. The *PLOD2* gene (3q23-24) encodes lysine hydroxylase 2 (LH2) [13]. In contrast to LH1, which functions as a helical LH, LH2 functions as a telopeptidyl LH to catalyze the hydroxylation of Lys residues in the collagen telopeptides, which is crucial for the formation of intermolecular cross-links in type I collagen [8,14,15]. Although FKBP65 does not have LH activity, BS1 also demonstrates dramatic underhydroxylation of telopeptide Lys and a subsequent decrease in the cross-linking of bone type I collagen, as is the case for BS2 [16,17]. Consistent with this, it was recently reported that FKBP65 mediates the dimerization of LH2, which is crucial for LH2 activity [11,18]. As of January 2023, 75 variants in *FKBP10* and 47 variants in *PLOD2* have been associated with BS or OI type XI, according to the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk).

Here, we report a case of moderately severe OI in a Chinese boy. Using WES and Sanger sequencing, we identified a compound heterozygous variation in the *FKBP10* gene, c.23dupG(p.S8Rfs*67)/c.825dupC(p.L275Rfs*95), of which c.23dupG was novel. Based on these findings, the patient was diagnosed with BS1 lacking congenital contracture or OI type XI with rare DI symptoms. Additionally, zoledronic acid treatment improved the vertebral deformity and BMD significantly in this patient.

2. Materials and methods

2.1. Subjects and ethics

The patient, a one and a half years old Chinese boy, was referred to Guangzhou Women and Children's Medical Center due to lumbar kyphosis. He also had a history of recurrent long bone fractures. Physical and radiographic examinations were performed. The study protocols were approved by the Human Ethics Committee of the Guangzhou Women and Children's Medical Center. Written informed consent was obtained from his parents.

2.2. Blood sample collection and DNA extraction

Peripheral blood was collected from the patient and his family members and stored in EDTA anticoagulant tubes at −80 °C. A Blood DNA Kit (D3392, Omega) was used to extract the genomic DNA (gDNA) according to the manufacturer's instructions. The concentration of gDNA was measured using a Qubit fluorometer (Thermo Fisher Scientific), and the integrity and purity of the samples were examined with agarose gel electrophoresis.

2.3. Whole-exome sequencing and genetic variant analysis

Whole-exome sequencing (WES) was performed at Chi Biotech (Shenzhen, China). Briefly, gDNA was sonicated into DNA fragments of 180–280 bp with a Covaris ultrasonicator. The construction of a DNA library and enrichment of human whole-exon DNA were performed with an Agilent Sure Select Human All Exon V6 kit according to the manufacturer's instructions. Paired-end 150 bp (PE150) fragments were sequenced with the Illumina HiSeq Xten System. Raw reads were collected using Illumina Base Calling software and then subjected to alignment with the reference genome (human_B37) using Burrows-Wheeler Aligner (BWA) and Samblaster. The alignment rate was 99.94%, the sequencing depth of the target region was 127 times, and the coverage of the target region was 99.53%. SAMtools was employed to detect single nucleotide variants (SNV) and indels (INDEL). ANNOVAR software was used to annotate these variants.

All variants were filtered following a previously described pipeline: 1) exclusion of variants with a frequency greater than 1% in any of the four databases (1000g_all, esp6500si_all, gnomAD_ALL and gnomAD_EAS), 2) exclusion of variants that were not in the coding (exonic) region or splicing region (splicing site ± 10 bp), 3) exclusion of synonymous SNPs that were predicted not to affect splicing, 4) retention of variants that were predicted by at least two of four prediction tools (SIFT, PolyPhen, MutationTaster, and CADD) to be deleterious and variants that were predicted to affect splicing [19].

2.4. Sanger sequencing

The *FKBP10* variants identified by WES were further confirmed with Sanger sequencing. The gDNA was used as a template. PCR primers were designed for each variant site: Forward-1 (GTGGGGCTAGTGTGTCTTGCAT) and Reverse-1 (GGATGGTAATTCTCCGGCGT) for c.23dupG; Forward-2 (GTCTTCCCAGCCCCCATTC) and Reverse-2 (CCAACCGGGGTTACCTTGAA) for c.825dupC. PCR was performed with high fidelity PrimeSTAR Max DNA Polymerase (Takara, Beijing, China). The amplified products

were sequenced by Shanghai Sangon Biotechnology (Shanghai, China). The *FKBP10* reference sequence was NM_021939.

2.5. Zoledronic acid treatment

The patient was given an intravenous infusion of zoledronic acid (0.1 mg/kg) in 250 ml 5% dextrose sodium chloride every 4 months since the age of one and a half when he was diagnosed with BS. After injection, a transient fever with a maximum temperature of 38 °C was observed. There were no other obvious adverse reactions after treatment.

3. Case presentation

The family pedigree is shown in Fig. 1A. Patient (II:3) was the third child of non-consanguineous Chinese parents. He visited our hospital at the age of one and a half due to lumbar kyphosis. He was born at term with a weight of 3250 g (50th percentile) and unknown length. The patient's developmental milestones were normal. Physical and radiographic examinations revealed a lumbar kyphosis deformity centered on the first lumbar vertebra (L1) but with no obvious scoliosis. Multiple lumbar vertebrae were flattened and wedge-shaped (Fig. 1B and C). Radiography revealed mild osteoporosis of the lumbar spine. No obvious abnormalities were found on the plain skull film. No limb deformities or joint contractures were observed (Fig. 1D). Facial features, hearing, intelligence, and sclera were normal. Notably, abnormal dentition was observed when the patient was three years old. The enamel of the maxillary incisors was partially exfoliated, indicating DI (Fig. 1E). In addition, the patient experienced multiple recurrent long bone fractures that began in infancy (Fig. 1F). At the age of 6 months, he sustained a right femoral fracture following a minor trauma, a left femoral fracture at 2 years of age, and bilateral tibial fractures at two and a half years old. The patient's serum levels of total alkaline phosphatase (ALP), calcium, phosphate, and vitamin D were normal. Based on these features, he was diagnosed with moderately severe OI. The patient's parents and family members exhibited no relevant clinical manifestations.

Zoledronic acid is a third-generation bisphosphonate bone resorption inhibitor that can inhibit osteoclasts, reduce bone turnover, and increase bone mass. It has been used to treat OI [20,21]. Thus, the patient was given an intravenous infusion of zoledronic acid (0.1 mg/kg) every 4 months beginning at one and half years of age. Two years later, when the patient was three and a half years old the vertebral deformity significantly improved, and the height of the lumbar vertebrae became normal (Fig. 1G). When the patient was 5

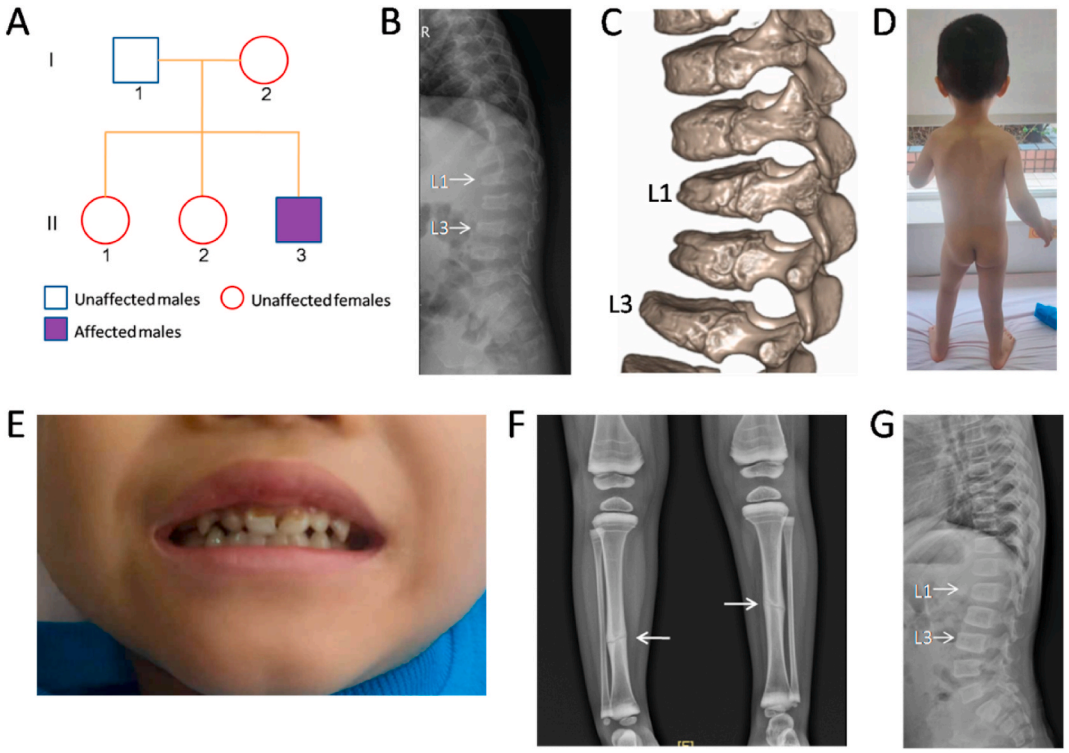

Fig. 1. Clinical presentations of an OI case. (A) The pedigree. II:3 is the patient. (B, C) X-radiographs and CT scanning demonstrated a lumbar kyphosis deformity centered on L1. Multiple lumbar vertebrae became flattened and wedge-shaped, especially L1 and L3. The X-ray film also showed mild osteoporosis in the spine. (D) No obvious limb deformities or joint contractures were found. (E) The enamel of multiple maxillary incisors was partially exfoliated, indicating DI. (F) The patient experienced multiple recurrent long bone fractures beginning in infancy. The X-ray film showed that he had bilateral tibial fractures (indicated by white arrows) at the age of 2 and a half. (G) Treatment with zoledronic acid improved the vertebral deformity significantly. Compared to before treatment (B), the height of lumbar vertebrae became normal.

years old, the patient's condition was relatively stable except for the deformity caused by an old fracture of the right tibia. The results of dual energy X-ray absorptiometry (DXA) indicated that BMD and its *Z*-scores at lumbar spine were higher than normal (BMD, 0.677 g/cm^2; *Z*-score, 3.6), which may reflect the positive effects of zoledronic acid treatment. There have been no further fractures since the age of two and a half.

To identify the genetic lesions causing OI, we performed WES using gDNA from the patient. A total of 123,185 genetic variants, including 111,194 SNPs (single nucleotide polymorphisms) and 11,991 Indels (small insertions or deletions, <50 bp), were initially detected. After variant filtering, 309 SNPs and 34 Indels remained (Fig. 2A). Among these, we found a compound heterozygous variation in the *FKBP10* gene: one base-pair duplication (c.23dupG) in exon 1 and one base-pair duplication (c.825dupC) in exon 5. Of the two variants, c.23dupG was not previously reported or found in the reference gene databases, including 1000 g_all, esp6500si_all, gnomAD_ALL and gnomAD_EAS. The frequency of c.825dupC was 0.03% in gnomAD_All database. No variants were found in the other genes related to OI. This finding was confirmed by Sanger sequencing, which showed that the patient's father carried a heterozygous c.825dupC and the mother carried a heterozygous c.23dupG (Fig. 2B). These variants were not detected in the patient's two sisters. Both variants were predicted to be disease-causing, resulting in a frameshift and a premature stop codon, leading to p.S8Rfs*67 and p.L275Rfs*95, respectively (Fig. 2C). According to the criteria of the American College of Medical Genetic and Genomics, the variant c.23dupG was classified as "likely pathogenic" with 1 very strong (PVS1) and 1 moderate (PM2) pathogenic evidence; c.825dupC was classified as "pathogenic" with 1 very strong (PVS1), 1 moderate (PM2), and 1 supporting (PP5) pathogenic evidence [22]. These results are consistent with the autosomal recessive inheritance pattern of BS or OI caused by these *FKBP10* variants.

4. Discussion

BS caused by *FKBP10* genetic variation is characterized by severe osteopenia and is mostly complicated by congenital joint contracture. In our study, we report a case of osteopenia, fragility fractures, and lumbar kyphosis, but no congenital joint contracture. Combined with the genetic analysis results showing that the patient harbored a novel compound heterozygous variation in the *FKBP10* gene (c.23dupG/c.825dupC), the patient was diagnosed with BS1 lacking congenital joint contracture or OI type XI. Notably, this patient exhibited abnormal dentition, indicating DI, which has rarely been reported in patients with BS caused by *FKBP10* variants.

Both c.23dupG and c.825dupC were predicted to be disease-causing, resulting in a frameshift and a premature stop codon, leading

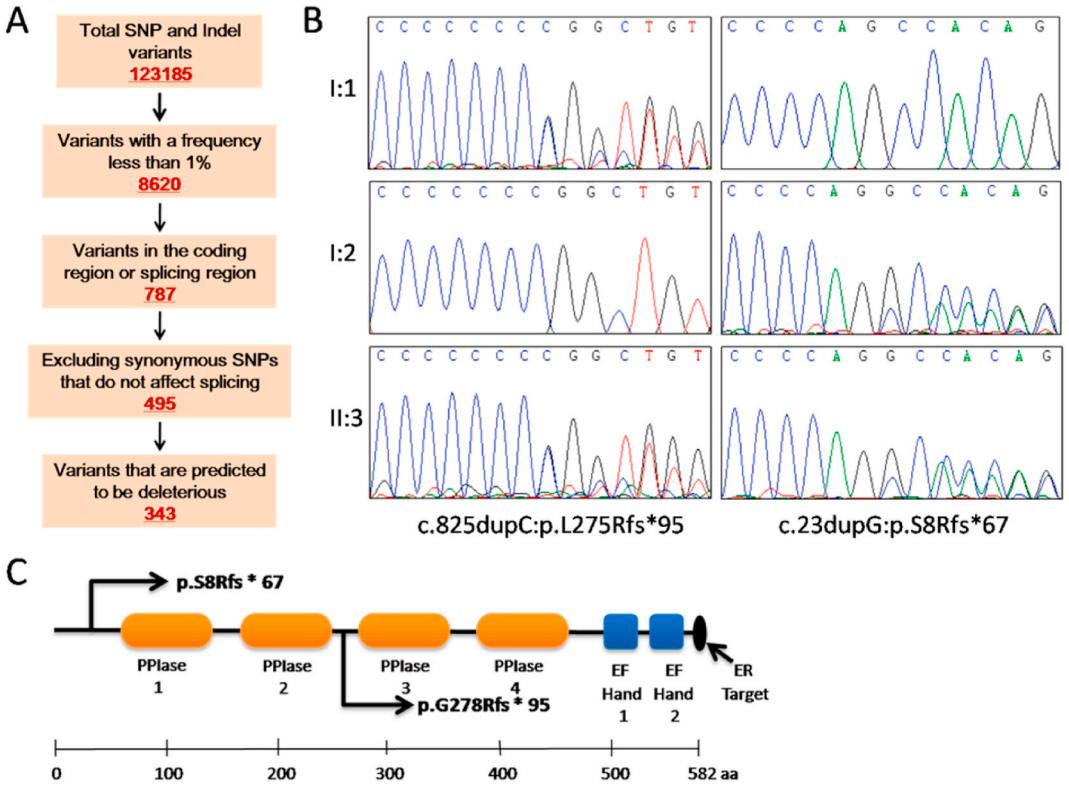

Fig. 2. Identification of a novel compound heterozygous variation in *FKBP10* gene. (A) Schematic representation of the filtering process of WES data. (B) Sanger sequencing. A novel compound heterozygous variation in *FKBP10* gene, c.23dupG/c.825dupC, were identified in the patient (II:3). The patient's father (II:1) carries heterozygous c.825dupC and mother (II:2) carries heterozygous c.23dupG. (C) Representation of FKBP65 protein with the location of variants. FKBP65 protein contains four peptidyl-prolyl-isomerase domains (PPIase), two EF Hand domains, and a putative ER-retention sequence (ER Target).

to p.S8Rfs*67 and p.L275Rfs*95, respectively. Of these two variants, c.23dupG has not been previously reported; c.825dupC was identified recently in two Chinese OI patients who featured with congenital joint contractures, scoliosis, and recurrent fractures, but without DI [23]. More than 75 variants of *FKBP10* associated with BS or OI have been recorded. Approximately 70% of the cases caused by *FKBP10* variants present with congenital joint contractures. However, why not all BS patients manifest joint contractures and/or DI remains unclear. Even the same *FKBP10* variant may or may not cause congenital joint contracture. For example, three patients carrying homozygous c.831dupC were reported by Kelley et al., in 2011, two of whom had congenital joint contractures and one who did not [6]. Recently, a statistical analysis was performed to investigate OI/DI phenotype-genotype correlation in a large cohort of OI cases caused by *Col1A1* or *Col1A2* variants. Four DI hotspots were identified [24]. To reasonably predict the severity and progression of BS, we suggest that a similar study should be carried out to investigate the phenotype-genotype correlation in the disease in the future.

Bisphosphonates have been extensively used to treat OI to increase bone mineral density and reduce the incidence of fractures. Zoledronic acid is a third-generation bisphosphonate drug that can inhibit osteoclasts, reduce bone turnover, and increase bone mass. It has obvious efficacy and few side effects. Recently, it was reported that zoledronic acid also has the function to enhance osteogenic differentiation in patients with osteoporosis [25]. Data regarding the therapeutic effects of zoledronic acid treatment in BS patients are limited [21]. In our case, the wedge-shaped deformity of the vertebral body improved, the height of the lumbar vertebrae became normal, and BMD was increased with zoledronic acid treatment. There have been no further fractures since the age of two and a half. All of these findings indicate that zoledronic acid has a positive effect on BS caused by *FKBP10* variants. However, the efficacy and safety of a long term treatment with zoledronic acid in BS patients still remains to be evaluated in large-scale clinical studies in the future.

The variant c.23dupG leads to p.S8Rfs*67, which almost completely blocks the production of FKBP65 protein. c.825dupC leads to p.L275Rfs*95, resulting in a truncated FKBP65 containing the first two PPIase domains. Recently, it has been reported that FKBP65 PPIase activity is required for the dimerization of LH2 to potentiate the LH2-driven collagen cross-link switch [11,18]. Therefore, the truncated FKBP65 caused by c.825dupC may retain some function of driving LH2 dimerization, or have a dominant negative effect, which results in the phenotype variation. In addition, nonsense-mediated mRNA decay may result in very little protein being produced. In the future, a functional study about the mutant FKBP65 should be carried out in cultured fibroblasts or osteoblasts.

In summary, we report a rare case of BS and identify a novel compound heterozygous variation of *FKBP10*, c.23dupG/c.825dupC, further expanding the genetic etiology spectrum of BS. We also provide further evidence that zoledronic acid is effective in treating BS.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Liyuan Shang: Writing – original draft, Investigation. **Weizhe Shi:** Resources, Investigation, Data curation. **Yibo Xu:** Methodology, Investigation. **Tianying Nong:** Validation, Methodology, Investigation. **Xia Li:** Validation, Methodology, Investigation. **Zhaohui Li:** Methodology, Investigation. **Yanhan Liu:** Visualization, Data curation. **Jingchun Li:** Visualization, Data curation. **Ya-Ping Tang:** Project administration, Conceptualization. **Mingwei Zhu:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Hongwen Xu:** Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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