Case Report

Further Evidence of Early-Onset Osteoporosis and Bone Fractures as a New *FGFR2*-Related Phenotype

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Further Evidence of Early-Onset Osteoporosis and Bone Fractures as a New *FGFR2*-Related Phenotype

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Abstract: Background: primary osteoporosis in children and young adults often suggests a monogenic disease affecting bone microarchitecture and bone mineral density. While Osteogenesis Imperfecta (OI) is the most recognized genetic cause of recurrent fractures, many other genes involved in bone metabolism may contribute to osteoporosis. Among them, *FGFR2* plays a critical role in bone growth and development by regulating osteoblasts differentiation and proliferation, as well as chondrogenesis. Germline pathogenic *FGFR2* variants are typically associated with syndromic craniosynostosis, conditions not characterized by bone fragility or osteoporosis. A report by Dantsev et al. (2023), recently identified *FGFR2* as a potential cause of dominant early-onset osteoporosis and bone fractures in a family. **Methods**: We performed clinical exome sequencing in trio to investigate potential genetic causes of the observed phenotype. **Results:** We report the case of a child presenting with severe osteoporosis with multiple fractures, carrying a mosaic likely pathogenic *FGFR2* variant, absent in both parental samples. **Conclusions:** Our findings provide further evidence that *FGFR2* pathogenic variants can lead to a novel non-syndromic bone mineralization disorder, reinforcing the role of *FGFR2* in the pathogenesis of early onset osteoporosis.

Keywords: osteoporosis; *FGFR2*; FGF signaling; early-onset osteoporosis; osteogenesis; Osteogenesis Imperfecta

1. Introduction

Osteoporosis is characterized by reduced bone density and abnormal bone microarchitecture, leading to bone fragility and increased risk for fractures [1]. It is a complex disorder and can be secondary to other diseases with several risk factors having a role in the pathogenesis [2]. When occurring in childhood or young adulthood in absence of an underlying causative condition, osteoporosis can be related to a monogenic bone disease [3]; in fact, bone fragility is a key finding in several skeletal dysplasias [4]. In particular, the paradigm of skeletal dysplasia with bone fragility is Osteogenesis Imperfecta (OI), a group of hereditary connective tissue disorders with recurrent fractures as main clinical manifestation [5]. *COL1A1* and *COL1A2* mutations account for about 85-90% of cases of OI; despite this, many other genes (involved in collagen biosynthesis, bone mineralization, and osteoblast differentiation) have been identified as causative of OI or hereditary early onset osteoporosis, thus expanding the molecular mechanisms of bone fragility [6–8].

Recently, Dantsev and colleagues [2023] reported the case of a 13-year-old boy affected by osteoporosis and multiple fractures, with a family history of abnormal bone mineralization and fractures, carrying a heterozygous variant in the *FGFR2* gene [9].

Fibroblast growth factor receptor 2 (*FGFR2*) is a tyrosine kinase receptor belonging to a family that includes four high affinity receptors with a similar structure [10]. It is expressed in various

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tissues, and regulates many biological processes as cell proliferation, migration, survival and differentiation [11–13] with a key role in the development and growth of the skeleton [14]. In particular, *FGFR2* is involved in osteogenesis of cranial and long bones [15,16]. Moreover, studies in mice models revealed a critical role of both gain and loss-of-function *FGFR2* variants in balancing the proliferation and differentiation of osteoprogenitor cells [17–19].

Pathogenetic variants in *FGFR2* have been related to different phenotypes, with craniosynostosis as the main clinical finding in most of them. The main *FGFR2*-related phenotypes are summarized in Table 1 [20].

In this report, we describe the case of a patient affected by severe osteoporosis with multiple fractures and negative molecular tests in genes commonly associated with bone fragility. Through a broader exome analysis, we detected a mosaic likely pathogenic variant in *FGFR2*. These findings furtherly support that isolated primary osteoporosis could be a new *FGFR2*-related phenotype, as suggested by Dantsev et al., so expanding the spectrum of genes responsible for bone fragility [9].

Table 1. Autosomal dominant *FGFR2*-related phenotypes listed in OMIM.

Disease	Clinical signs	
Crouzon syndrome OMIM 123500	Craniosynostosis, hypertelorism, exophthalmos and external strabismus, hypoplastic maxilla, and prognathism	Syndromic craniosynostosis
Apert syndrome OMIM 101200	Craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet	Syndromic craniosynostosis
Pfeiffer syndrome OMIM 101600	Craniosynostosis syndrome with characteristic anomalies of the hands and feet.	Syndromic craniosynostosis
Saethre-Chotzen Syndrome OMIM 101400	Craniosynostosis, facial dysmorphism, and hand and foot abnormalities. Hearing loss, limb anomalies, short stature and vertebral fusions.	Syndromic craniosynostosis
Jackson-Weiss Syndrome OMIM 123150	Premature fusion of the cranial sutures as well as radiographic anomalies of the feet	Syndromic craniosynostosis
Antley-Bixler Syndrome without genital anomalies or disordered steroidogenesis OMIM 207410	Craniosynostosis, radio-humeral synostosis, midface hypoplasia, choanal stenosis or atresia, and multiple joint contractures.	Syndromic craniosynostosis
Beare-Stevenson cutis gyrata syndrome OMIM 123790	Furrowed skin disorder of cutis gyrata, acanthosis nigricans, craniosynostosis, craniofacial dysmorphism, digital anomalies, umbilical and anogenital abnormalities, and early death. Cloverleaf skull can be observed.	Syndromic craniosynostosis
Bent bone dysplasia Syndrome OMIM 614592	Poor mineralization of the calvarium, craniosynostosis, dysmorphic facial features, prenatal teeth, hypoplastic pubis and clavicles, osteopenia, and bent long bones	Lethal skeletal dysplasia, syndromic cranyiosynostosis
LADD syndrome 1 OMIM 149730	Affecting llacrimal glands and ducts, salivary glands and ducts, ears, teeth, and distal limb segments.	Multiple congenital anomaly disorder

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2. Results

2.1. Clinical Description

The boy is the first child of healthy non-consanguineous parents. No other family members showed signs of Osteogenesis Imperfecta and no early onset osteoporosis or skeletal dysplasia cases in the family have been referred.

Natural childbirth occurred at 37 weeks of gestation (weight: 3680 g, length: 52 cm, Apgar score: 9-10). The main milestones in early psychomotor development were at appropriate ages.

The child underwent investigations at 5 years and 4 months for knee pain and gait anomalies in the absence of trauma history or signs of infection. X-ray showed reduced mineralization and metatarsal abnormalities. Idiopathic arthritis was initially suspected.

The first bone fracture (non-traumatic fracture of left distal tibial metaphysis) occurred at age 6. At 7 years old, the proband presented D3-D4-D5 vertebral compression fractures, with reduction of all but one thoracic vertebral body high, and bilateral VII rib non-traumatic fractures. He presented lower limbs pain and used to walk with aids. Clinical presentation and personal history were suggestive of a bone mineralization disorder. X-rays performed at chest, femur, dorsal column, and right hand revealed a reduced bone density (Figure 1). Dual-energy X-ray absorptiometry (DEXA) showed a Z-score = -3 at lumbar level and total body Z-score = -1.6.

Glomerular and tubular renal functions were normal. Celiac disease markers, rheumatoid factor and ANA were all negative. Metabolic tests including plasma acylcarnitine, urinary organic acids, amino acids and urinary mucopolysaccharides were normal. No alterations were reported in the calcium-phosphorus metabolism, in the thyroid function, in ACTH and cortisol values, in the GH-IGF1 axis, in blood gas analysis and muscle enzymes. In addition, the evaluation of biochemical markers for bone status assessment revealed normal osteocalcin but markedly altered values of C-terminal telopeptide (CTX) (1175 pg/ml) and procollagen type 1 N-terminal propeptide (P1NP) (455 mcg/l). Other markers values were: serum calcium 9.6 mg/dl, serum phosphate 5.6 mg/dl, PTH 15 pg/ml, urinary calcium 37.9 mg/dl, alkaline phosphatase 285 U/l, bone alkaline phosphatase 63.2 mcg/l).

Cardiac and abdominal ultrasound revealed no abnormalities, with the only exception of accessory spleen. Considering the fracture history and the DEXA results, quarterly bisphosphonate infusions (Neridronate) were started.

Despite treatment, the child underwent other fractures: femoral neck for minor trauma (7 years), diaphyseal stress fracture of right tibia (7 years and 6 months), diaphyseal fracture of right radius (8 years), and pathological right femur fracture surgically treated (8 years and 8 months). Due to the lack of clinical benefit, the bisphosphonate therapy was suspended after approximately two years.

Currently, at 11 years old, the proband walks indoor with a walker and outside with a wheelchair, practicing only a few steps on his own. Hydrotherapy is performed 1 day/week and physiotherapy 2 hours/week. He visits the emergency room monthly for musculoskeletal pain not responding to paracetamol, NSAIDs (nonsteroidal anti-inflammatory drugs), magnesium and pregabalin. At clinical examination the boy weighs 45 Kg (90°pct) and is 130 cm tall (25-50°pct), with a BMI = 26.6 (mild obesity). He presents shortened trunk due to vertebral deformity, dorso-lumbar hyper lordosis and dorsal kyphosis in reduction, protruding abdomen, valgus knee, tibia varus, pronated feet, soft skin, mild hypotonia, and mild joint hyperlaxity, especially at the hips, with a Beighton score = 4.

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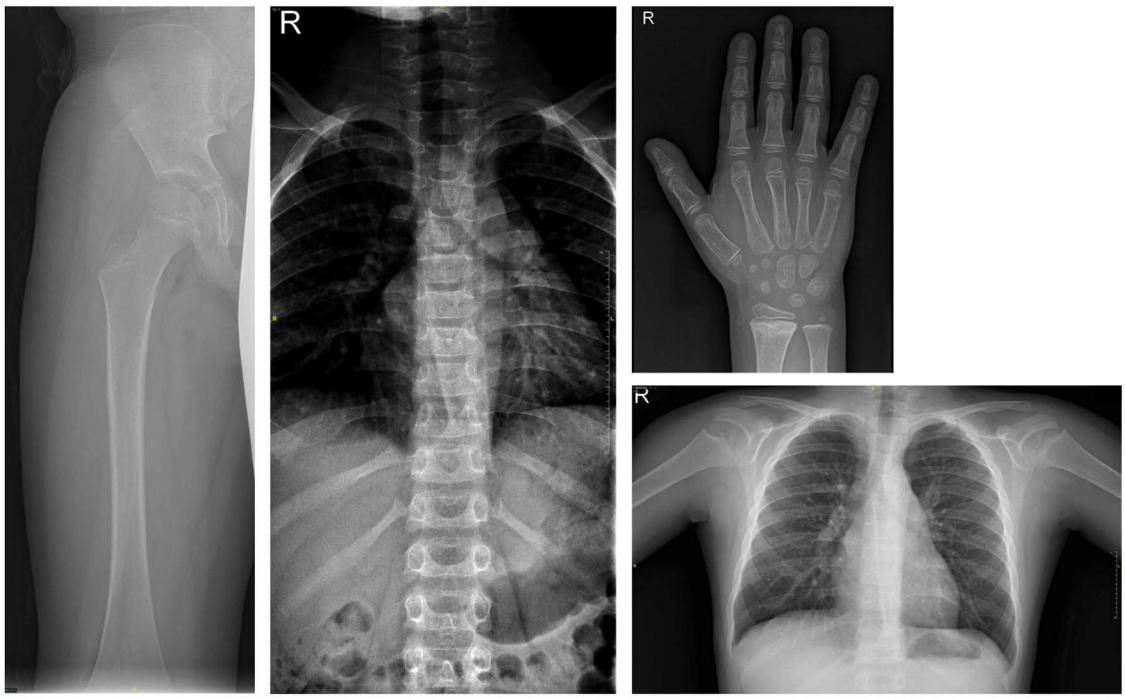

Figure 1. X-rays at 7 years old. Chest, femur, spine, and right hand X-rays revealed reduced bone density.

2.2. Molecular Findings

To better delineate the clinical presentation, genetic tests were performed with parents' written informed consent. DNA was extracted by peripheral blood sample and analyzed by Next Generation Sequencing for the presence of pathogenic variants, initially focusing on the genes related to Osteogenesis Imperfecta and Hypophosphatasia, which resulted negative, and then on all the known disease-associated genes.

The clinical exome analysis revealed the presence of the mosaic (~30%) variant c.1262G>A p.(Arg421His) in *FGFR2* gene (NM_000141.5). The variant has an allele frequency of 0.000003977 in the GnomAD database (https://gnomad.broadinstitute.org/), it has never been reported in scientific literature, and it is predicted as deleterious and probably damaging by Mutation Taster and PolyPhen 2.0 with a 31 CADD score; according to the ACMG criteria (PP2 + PP3 + PS2), the variant is classified as likely pathogenic (class 4).

3. Discussion

Bone development and homeostasis are complex processes, and the delicate balance between bone formation and resorption is crucial for maintaining skeletal integrity and preventing conditions such as osteoporosis [1]. Genetic alterations in the elements involved in this balance can lead to skeletal disorders characterized by bone fragility, of which Osteogenesis Imperfecta represents the paradigm; however, not all patients with an OI phenotype harbor causative mutation in known OI-related genes or in other genes commonly associated with bone fractures [5]. Moreover, several atypical forms of OI have been described, and many other mineralization disorders have been defined in the latest nosology [4], thus complicating the clinical characterization and differential diagnosis of patients with recurrent fractures. Recent studies have further advanced our understanding of bone mineralization disorders by uncovering novel causative genes involved not only in collagen biosynthesis and folding but also in other molecular pathways regulating bone development and homeostasis [5].

Herein we describe a patient with bone fragility and severe early onset osteoporosis carrying a mosaic likely pathogenic variant in *FGFR2*. For our knowledge, this is the second report of early onset

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osteoporosis in presence of a *FGFR2* variant. In both our patient and the earlier report [9] the clinical phenotype initially suggested a diagnosis of Osteogenesis Imperfecta, but molecular investigations did not reveal any pathogenic variant in OI- or bone fragility-related genes. In the previous report, the c.722dup *FGFR2* variant was identified in a young boy with recurrent fractures beginning from infancy, low BMD, joint pain, dental caries and headaches. The same variant was also present in the father, who had low-impact fractures, and in the sister, who presented genu valgum, hip dysplasia, scoliosis and dental caries but no fracture history [9].

FGFR2 is a tyrosine kinase receptor mainly expressed in the epithelial and mesenchymal cells, playing a key role in the development of endocrine glands, skeleton, as well as skin and other organs [21]. It is known to regulate the development of osteoblasts and an increased FGFs/FGFRs-dependent signaling can lead to hyperplasia of immature osteoblasts, inhibit their differentiation and trigger apoptosis, causing imbalance between osteosynthesis and bone resorption [11]. Recent findings also suggest that FGFR2 may contribute to chondrocytes development [12].

FGFR2 pathogenic variants are primarily associated with skeletal dysplasias with craniosynostosis as a key feature, but bone fragility and osteoporosis are not typically considered common characteristics. In fact, the function of *FGFR2* signaling is well established in the craniofacial skeletal development [14,15], whereas its role in the appendicular skeleton remains less understood.

Notably, mineralization defects and long bone deformities are indeed hallmarks of Bent Bone Dysplasia (OMIM #614592), a lethal *FGFR2*-related disease characterized by high perinatal lethality, bent long bones, osteopenia, craniosynostosis, and dysmorphic facial features. Studies suggest that impaired FGF signaling underlies these skeletal abnormalities, as indicated by reduced plasma membrane levels of *FGFR2* and decreased receptor responsiveness [22]. Similarly, mouse models carrying specific *FGFR2* splice variants exhibit delayed mineralization of the calvarium, craniosynostosis, and shortened long bones, reinforcing the hypothesis of a *FGFR2* role in bone formation [19].

Other in vitro and mouse models studies have demonstrated that *FGFR2* is a regulator of bone construction, stimulating osteoprogenitor cell proliferation and differentiation, and contributing to intramembranous bone formation and ossification processes [23]. These findings provide a plausible explanation for the mineralization defects observed in Bent Bone Dysplasia and align with the phenotype observed in our patient. Moreover, population studies have suggested an association between *FGFR2* variants and increased susceptibility to osteoporosis [24–27].

The molecular mechanism underlying the variable phenotypes associated to mutations in *FGFR2* is not completely understood, but a few genotype-phenotype correlations have been identified. Loss of function *FGFR2* mutations in the tyrosine kinase domain are responsible for Lacrimo-auriculo-dento-digital syndrome (LADD, OMIM #123790), which is characterized by lacrimal duct aplasia, hearing loss, dental abnormalities and digital malformations [28]. On the other hand, loss of function missense *FGFR2* variants in the trans-membrane (TM) domain have been found in Bent Bone Dysplasia [22]. The other syndromic *FGFR2* diseases are apparently caused by gain-of function variants, leading to constitutive receptor activation or altered ligand specificity [14].

Our patient presents early onset osteoporosis with recurrent fractures, joint pain, limb deformities and impaired ambulation. He harbors a mosaic missense variant in *FGFR2*, probably related to the phenotype; however, in the absence of functional studies, we cannot exclude a different genetic or complex cause of the disease. The reported phenotype partially overlaps with the one described in the family by Dantsev and colleagues.

The phenotype observed in our patient only partially overlaps with the Dantes and colleagues' case, with fractures and osteoporosis as shared features. However, significant clinical variability was also reported among the previously described individuals, highlighting the variable clinical effects of these genetic alterations [9]. Furthermore, the variant we identified is a mosaic missense mutation, which may account for the phenotypic differences between the two reports. Moreover, given the different location and type of variant, it is not possible to draw conclusions regarding a potential genotype-phenotype correlation.

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Further investigations are required to elucidate the molecular mechanism and pathways underling FGFR2 signaling and its role in various phenotypes, including bone mineralization defects. Clarifying the mechanism leading to bone mineralization disorder related to *FGFR2* and understanding its role in bone development and growth could also provide new insights to address new therapeutic approaches [29], as well as revealing new molecular mechanisms in OI has been the starting point for new targeted therapies [29].

4. Materials and Methods

After obtaining informed consent for the genetic analyses, clinical exome enrichment and parallel sequencing were performed on genomic DNA extracted from patients and parents' circulating leukocytes. Library preparation and clinical exome capture were performed by using the Twist Custom Panel (clinical exome - Twist Bioscience) according to the manufacturer's protocol and sequenced on the Illumina NovaSeq 6000 platform. The BaseSpace pipeline and Geneyx software (LifeMap Sciences) were, respectively, used for variant calling and annotation. Sequencing data were aligned to the hg19 human reference genome. The functional impact of the variants was analyzed by Combined Annotation Dependent Depletion (CADD) V.1.3, Sorting Intolerant from Tolerant (SIFT), and Polymorphism Phenotyping v2 (PolyPhen-2). Rare variants (MAF < 0.1%) were filtered based on the gnomAD database. Based on the guidelines of the American College of Medical Genetics and Genomics, a minimum depth coverage of 30X was considered suitable for analysis. Variants were examined for coverage and Qscore (minimum threshold of 30) and visualized by the Integrative Genome Viewer (IGV).

5. Conclusions

Here, we describe the case of a child with severe osteoporosis and multiple fractures, carrying a mosaic likely pathogenic *FGFR2* variant. This report provides further evidence supporting osteoporosis as a new distinct phenotype associated with *FGFR2* variants. Our findings highlight the need for further investigations to unravel the role of *FGFR2* in bone development and growth. A deeper understanding of the molecular mechanism by which *FGFR2* contributes to osteoporosis could pave the way for identifying novel therapeutic targets for skeletal disorders characterized by bone fragility or multifactorial osteoporosis.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy, legal, and ethical reasons.

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