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Case Report

A case of neonatal osteofibrous dysplasia with novel CDK12 and DDR2 mutations

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ABSTRACT

Osteofibrous dysplasia [OFD] is a rare, benign pediatric fibro-osseous lesion that exclusively arises in the lower limbs. Apart from the limited number of familial OFD cases with MET mutation, no other genetic aberrations have been identified. Herein, we report a case of OFD in a four-month- old girl's leg with novel cyclin-dependent kinase 12 and discoidin domain receptor 2 gene mutations. Further studies to understand their role in the pathogenesis and clinical utility are needed.

1. Introduction

Osteofibrous dysplasia [OFD] is a rare, benign pediatric fibro-osseous lesion that exclusively arises in the tibia with or without co-involvement of the ipsilateral fibula (Czerniak, 2016, 3). A limited number of neonatal/ infantile cases of osteofibrous dysplasia have been reported (Karol et al., 2005; Sunkara et al., 1997; Castellote et al., 1988; Smith et al., 1991; Anderson et al., 1993; Hindman et al., 1996; Teo et al., 2007; Zamzam, 2008; Çetinkaya et al., 2012; Kim and Lee, 2015; Jobke et al., 2014; Sarisozen et al., 2005). Patients with osteofibrous dysplasia present with gradual leg swelling, anterior bowing, and pathologic fractures in advanced cases. Most cases of osteofibrous dysplasia behave favorably (Jobke et al., 2014; Park et al., 2018). The genetics and etiology of osteofibrous dysplasia remain largely unknown. Unlike fibrous dysplasia [FD], patients with osteofibrous dysplasia do not harbor guanine nucleotide-binding protein *[GNAS]* mutations (Nielsen et al., 2020) and apart from the familial osteofibrous dysplasia cases with MET mutation, no other genetic aberrations have been reported (Nielsen et al., 2020). Discoidin domain receptor 2 *(DDR2)* is a tyrosine kinase receptor that is a part of discoidin domain containing receptors family. It is expressed in different tissues during development and adult life. *DDR2* missense mutations have been associated with rare skeletal disorders (Bargal et al., 2009; Ali et al., 2010) and is involved in tumorigenic processes in a variety of cancers (Rammal et al., 2016; Henriet et al., 2018). Cyclin-dependent kinase 12 *(CDK12)* is a member of transcription-associated CDK subfamily that regulate transcription of genes involved in physiological cellular DNA damage response and embryological development (Paculová and Kohoutek, 2017; Juan et al., 2016). A role for *CDK12* in tumorigenesis has emerged in different types of malignancies including sarcomas.

To the best of our knowledge, none of these two genes have been reported in cases of OFDs. Herein, we report a case of alarming leg swelling in a female baby that was diagnosed as neonatal osteofibrous dysplasia with novel *CDK12* and *DDR2* gene mutations.

2. Case

A 4-month-old girl presented to the orthopedic clinic with progressive left lower limb-deforming bony swelling that was first noticed shortly after birth with reduced limb movement. The lesion was clinically alarming for a malignant process. On clinical examination, there were no dysmorphic features, skin pigmentation, or associated local skin erythema; however, tenderness was noticed. The patient's weight and weight were normal for the age and gender. Laboratory markers, including serum α-fetoprotein, C-reactive protein levels, the erythrocyte sedimentation rate, and microbiological cultures, were unremarkable.

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X-ray and magnetic resonance imaging (MRI) revealed a well-defined expansile lucent lesion within the distal diaphysis of the left tibia with a rim of sclerosis and a mild periosteal reaction measuring 2.7 cm in the greatest dimension. Another similarly appearing eccentric, oval-shaped, 1-cm lesion was noted at the fibula distally (Fig. 1). The findings of abdominal ultrasound eliminated the possibility of intra-abdominal/retroperitoneal malignances.

Biopsy of the tibia disclosed a moderately cellular lesion comprising irregular woven bone trabeculae rimmed with bland osteoblasts and few osteoclasts with intertrabecular bland fibrous proliferation but no epithelial cell clusters or increased mitosis, atypia, or necrosis (Fig. 2A and B). Rare spindle cells stained positively for cytokeratins (Fig. 2C), whereas they were negative for rhabdomyoblastic markers (desmin and myogenin) and histiocytic markers (CD68, CD1a, and S100). Interphase fluorescence in situ hybridization [FISH] for the rearrangement of ETV6 gene at chromosome 12p13 (Vysis ETV6 Break Apart FISH Probe Kit; Abbott) was done and it was negative, which eliminated the remote possibility of congenital fibrosarcoma (Fig. 2D).

The specimen was sequenced using a targeted, next generation sequencing (NGS) assay (Oncomine™ Comprehensive Assay v3 GX, ThermoFisher Scientific) to clarify whether the lesion harbored guanine nucleotide-binding protein (GNAS) or MET mutations. The assay enables the detection of relevant SNVs, CNVs, gene fusions, and indels from 161 unique genes on Ion Torrent Genexus Integrated Sequencer. Thermo Fisher Scientific' Ion Torrent Oncomine Reporter software (4.2.1 data version 2019) was used in analysis and report generation. Presented data was compared to published database by Thermo Fisher Scientific (version 2019.03(009)). Only variants having an allelic frequency of the assayed tumor DNA at 5 % or higher are reported. Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines. The GNAS gene was not mutated, which combined with the histologic features made a diagnosis of fibrous dysplasia (FD) unlikely and favored a diagnosis of osteofibrous dysplasia (OFD). Interestingly, in addition to the wild type of MET gene, novel missense mutations were detected in the discoidin domain receptor 2 (DDR2; c.2068A > G) and cyclin-dependent kinase 12 (CDK12; c.1462G > A) genes (variants details are provided in Table 1).

To explore the possible impact of these amino acid substitutions on the structure and predict their functional effect on the protein, polymorphism phenotyping tools like Poly Phen-2 (v2.2.2r406, Adzhubei et al., 2010) and FATHMM (v2.3, Shihab et al., 2013) were used. DDR2 protein (UniProt entry: Q16832, NP_006173.2) contains two domains; Coagulation factor 5/8 type C-terminus (Cys30 – Cys185) and Kinase domain (Leu563 – Leu849). The identified M690V mutation in DDR2 gene occurred at the kinase domain and is most likely damaging in nature as predicted by the HumDiv and HumVar scores of 0.908 and 0.740, respectively, in the Polymorphism Phenotyping tool (v2.2.2r406) (Fig. 3). FATHMM also reports a score of −2.38 with the potential involvement of this mutation in numerous inherited diseases such as cancer and nervous system diseases. On the other hand, CDK12 protein (UniPort: Q9NYV4, NP_057591.2) has a single kinase domain that spans from Phe727 – Leu1020, hence E488K mutation is most likely to be benign in nature by Poly Phen-2 (Fig. 3). Furthermore, FATHMM score for the variant was 1.04 which suggests that effects of this mutation were well tolerated by the protein.

The patient was managed conservatively with mass curetting and backslab cast immobilization. Follow-up for more than one year revealed a reduction in tumor size and normal lower limb function and development.

3. Discussion

OFD is a rare, benign fibro-osseous lesion of the bone that was first described by Frangenheim in 1921 as "osteitis fibroma" and subsequently classified by Jaffe as a rare intracortical variant of FD (Karol et al., 2005). In 1976, Campanacci proposed the term *osteofibrous dysplasia* to introduce this entity as a separate disease (Czerniak, 2016). OFD accounts for less than 1 % of all bone tumors with no clear sex predilection, and it characteristically affects the anterior mid-cortex of tibia with or without fibular involvement (Czerniak, 2016) Ipsilateral involvement of fibula is reported in 20 % of OFD cases (Nielsen et al., 2020). Bilateral OFD and OFD in other bones such as humerus, radius, and ulna, although rare, have been reported (Karol et al., 2005, Sunkara et al., 1997). OFD generally affects children younger than 10 years of age; however, it is rarely seen in neonates. A literature review revealed 13 cases of neonatal OFDs (Karol et al., 2005; Sunkara et al., 1997;

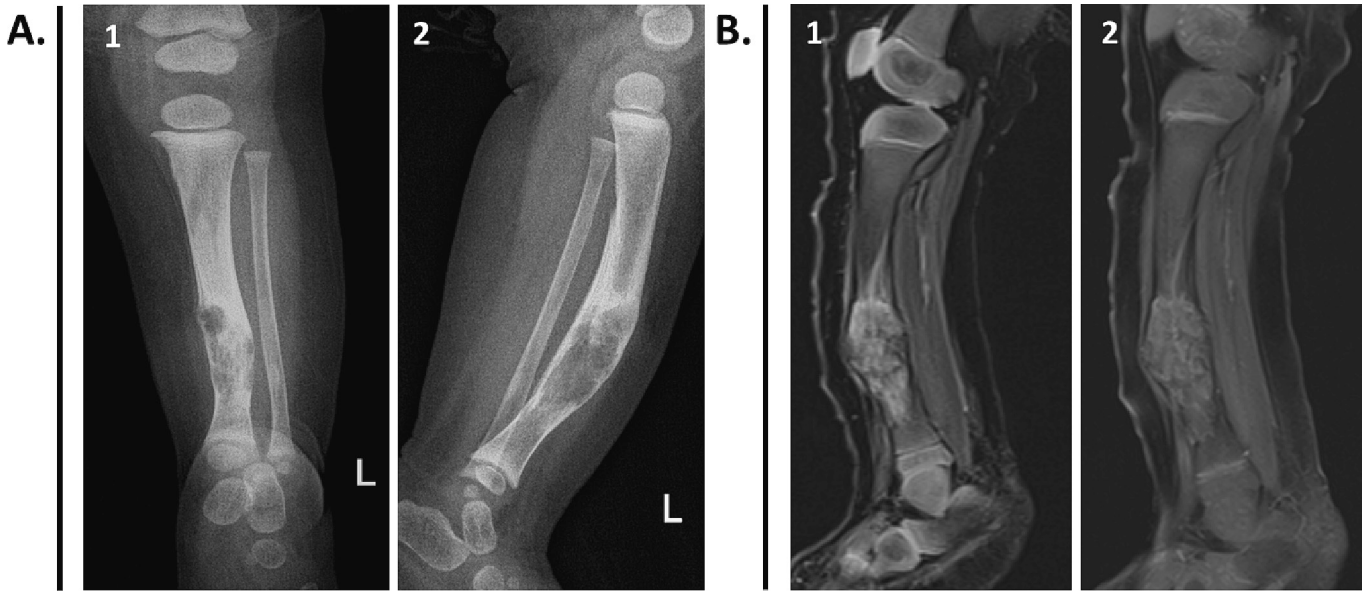

Fig. 1. A. X-ray: frontal [A.1] and lateral [A.2] radiographs. A well-defined expansile lucent lesion within the distal diaphysis of the left tibia [1.3 × 1.2 × 2.7 cm]. There is a rim of sclerosis around the lesion and mild periosteal reaction. Another similarly appearing intramedullary eccentric, oval-shaped lesion [1 × 0.4 × 0.3 cm] noted at the fibula distally. B. Magnetic resonance imaging [MRI]; Sagittal T2 fat suppressed MRI [B.1] and post contrast T1 weighted fat suppressed MRI [B.2] demonstrates well-defined lesion involving both the cortex and medullary cavity at the distal diaphysis of the left tibia with no aggressive cortical breakthrough or associated soft tissue mass component.

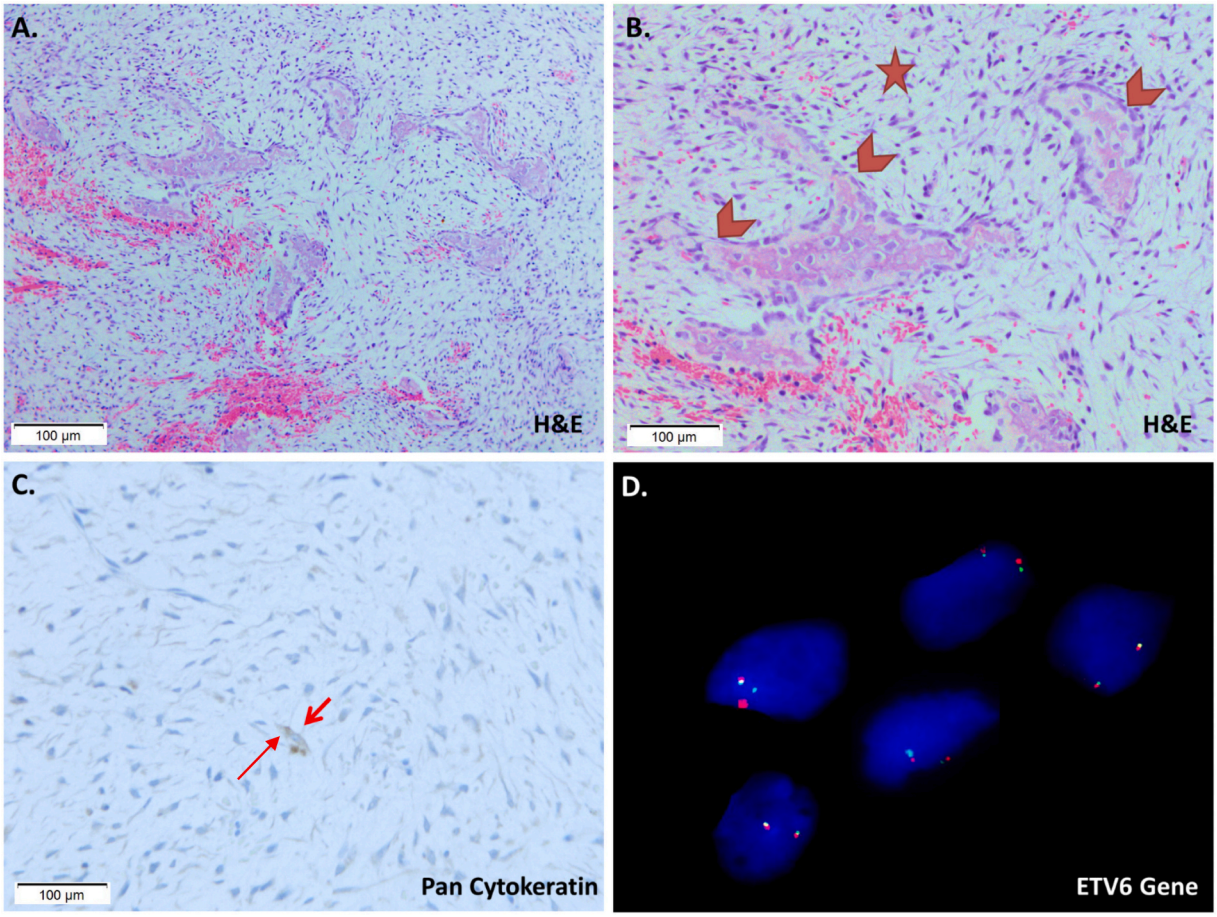

Fig. 2. Microscopic appearance and ancillary tests. A and B. Bland fibrous proliferation in storiform pattern (*) filling intertrabecular spaces with new irregular bone trabeculae rimmed with bland osteoblasts (arrow heads, H& E stain, 10× and 20×). C. Rare spindle cells positive for pancytokeratin (arrow, PanCK immunohistochemistry, 20×) by immunohistochemistry. D. ETV 6 gene is normal [FISH].

Table 1
DDR2 and CDK12 gene variants details.

Gene	Amino acid change	Coding	Locus	Allelle frequency	Transcript	Variant effect	dbSNP ID	Cosmic ID
DDR2	p.(M690V)	c.2068A>G	chrl:162745945	54.60 %	NM_006182.2	Missense	rs377626332	–
CDK12	p.(E488K)	c.1462G>A	Chrl71:37627547	33.66 %	NM_016507.3	Missense	rs774921821	COSV71001177

Castellote et al., 1988; Smith et al., 1991; Anderson et al., 1993; Hindman et al., 1996; Teo et al., 2007; Zamzam, 2008; Çetinkaya et al., 2012; Kim and Lee, 2015; Jobke et al., 2014; Sarisozen et al., 2005). In the reported cases, the median age at diagnosis was three days (ranging from 0 to 35 days) with a median tumor size of 3 cm (ranging 2–8 cm). There appeared to be male predominance (~67 % of cases). The most common presenting symptom was limb swelling and pain. Five cases (~42 %) were associated with pathologic fracture. One case was associated with familial and bilateral disease. Clinical presentation, management, and outcome are summarized in Table 2.

On imaging, OFDs are typically located at the diaphysis at the anterolateral cortex of the tibia, resulting in multi-loculated, well-demarcated expansile radiolucent lesion that is often oriented parallel to the shaft. Anterior bowing deformity is frequently present at the time of diagnosis. Additional findings of pathological fracture can be observed in some cases (Czerniak, 2016). The cortical origin of the lesion might be difficult to ascertain in neonates on radiographs (Czerniak, 2016). Lesions are typically hot in bone scans, which is a pitfall for an infectious or malignant process (Nielsen et al., 2020).

In a properly sampled specimen, a zonal architecture of the lesion can be appreciated microscopically. The center of the lesion comprises a storiform bland fibrous spindle cell proliferation admixed with irregularly woven bone trabeculae that are rimmed by prominent osteoblasts. The bone trabeculae mature into anastomosing the bone at the periphery (Czerniak, 2016; Nielsen et al., 2020). None or rare single-scattered, keratin-positive cells can be seen by immunohistochemistry. Pathologic findings such as hemorrhage, fracture, and repair, can complicate the microscopic evaluation when present. OFD should be differentiated from FD and OFD-like adamantinoma. FD is an intramedullary lesion that contains more cellular stroma. Prominent osteoblastic rimming and single keratin-positive cells are typically absent in FD cases. OFD-like adamantinoma can be difficult to differentiate from OFD as it occurs exclusively in the tibia as well. However, OFD-like adamantinoma tends to show small, clusters of keratin-positive cells that comprise at least three cells (Nielsen et al., 2020).

The pathogenesis of OFD is unknown, but the presence of trisomies of chromosomes 7, 8, and 12, which are also present in adamantinoma, suggest a neoplastic process (Czerniak, 2016; Nielsen et al., 2020).Genetic abnormalities have been found in a minority of the spindle cell component of the tumor but not in the osteoblasts (Gleason et al., 2008).

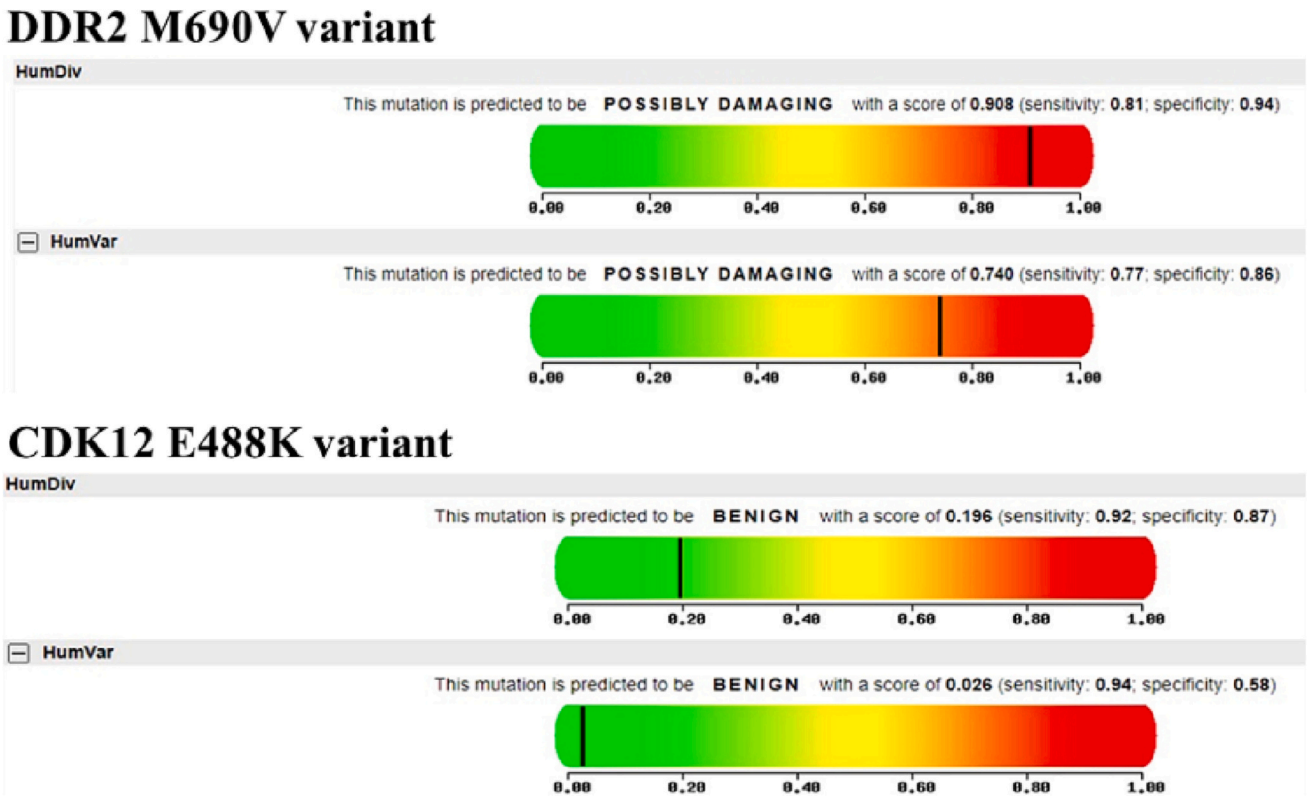

Fig. 3. Polyphen-2 scores for DDR2 and CDK12 variants. Generated by Polymorphism Phenotyping tools Poly Phen-2 (v2.2.2r406, Adzhubei et al., 2010).

Unlike FD, which harbors postzygotic missense mutation in guanine nucleotide-binding protein (GNAS) gene in up to 90 % of cases, OFDs do not (Tabareau-Delalande et al., 2013). Nevertheless, the test was performed to rule out the possibility of lesion under sampling. Recently, germline and somatic mutations in MET receptor tyrosine kinase pathways, which are involved in the osteogenesis regulation at the diaphysis, have been identified in three families with an autosomal-dominant form of OFD and in one subject with bilateral disease (Gray et al., 2015). NGS demonstrated that our case did not have GNAS or MET mutations, instead, novel missense mutations in DDR2 (c.2068A > G) and CDK12 (c.1462G > A) genes were detected.

Discoidin domain receptor 2 (DDR2) is a tyrosine kinase receptor and part of discoidin domain containing receptors family that include DDR1 and DDR2 receptors and recognize collagen as their ligands. DDRs are expressed in different tissues during development and adult life. DDR2 is expressed in connective tissues and plays a physiological role in bone growth as DDR2 knockout mice showed abnormal chondrocytes proliferation, dwarfism, and short bone (Leitinger, 2014). In humans, DDR2 missense mutations have been associated with a rare skeletal disorder known as spondylo-meta-epiphyseal dysplasia, with short limbs and abnormal calcifications (SMED-SL) (Bargal et al., 2009; Ali et al., 2010). Dysregulated DDR2 is also involved in tumorigenic processes like epithelial to mesenchymal transition and invasion in a variety of cancers (Rammal et al., 2016; Henriet et al., 2018). According to OncoKB™ data base, no alterations that may predict response to a targeted drug therapy have been reported yet (Chakravarty et al., 2017).

Cyclin-dependent kinase 12 (CDK12) is a member of transcription-associated CDK subfamily that includes CDK7, 8, 9, 11, and 13. They regulate transcription of genes involved in physiological cellular DNA damage response, differentiation, and embryological development (Paculová and Kohoutek, 2017; Juan et al., 2016; Lui et al., 2018). A role for CDK12 in tumorigenesis has recently emerged. According to The Cancer Genome Atlas [TCGA], different malignancies, including sarcomas, were linked to CDK12 alterations (Lui GYL, 2018). COSMIC database shows that out of 697 malignant bone tumors, CDK12 was mutated in two; Ewing sarcoma and telangiectatic osteosarcoma (0.29 %) (Tate et al., 2019). Finally, the CDK12 status has a potential therapeutic utility in cancer patients (Paculová and Kohoutek, 2017; Lui et al., 2018). Since CDK12 plays a central role in controlling DNA damage response and promoting homologous recombination repair, inhibiting CDK12 would induce a cellular synthetic lethality and enhance sensitivity to DNA cross-linking agents and poly (ADP-ribose) polymerase (PARP) inhibitors. The PARP inhibitor olaparib is an FDA-approved agent for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) with deleterious germline or somatic CDK12 mutations. However, not all CDK12 mutations may have the same biologic effects (Cerami, 2012; Gao, 2013). In our literature review, we could not find any reports of OFDs cases that harbor either DDR2 or CDK12 mutations. To the best of our knowledge, this is the first report detecting these mutations in an OFD case. Clearly, it is premature to assume that these aberrations are central to OFD pathogenesis, and examination of a larger number of cases is needed to establish whether these are recurrent genetic phenomena and their role, if any, in disease evolution.

In general, OFD has a favorable prognosis. Most lesions gradually expand during the first 5–10 years and stabilize at the time of skeletal maturity, and some can spontaneously regress after puberty or biopsy (Jobke et al., 2014; Park et al., 2018). A large study, in which the outcome of 55 tibial OFD cases was documented with a mean follow up of 91 months (18–233 months), showed that in 35 cases (63 %), observation/conservative management was sufficient while surgical intervention was needed in only 20 cases (36 %) (Park et al., 2018). The disease natural behavior in the observation-only group showed that 24 cases had stable disease; 11 cases had growing lesions, 10 of them had it before reaching skeletal maturity and 1 after reaching skeletal maturity. Indication for surgical intervention include pain, recurrent fracture, lesions increasing in size after skeletal maturity, or large size before skeletal maturity. Surgical management included curettage and excision

Table 2
Summary of neonatal OFDs case reports with clinical presentations and outcomes.

Reference	Age at presentation	Gender	Location	Management	Outcome	Associated pathological fractures	Tumor size (cm)
Castellote et al. (Castellote et al., 1988)	7 days old	Male	- Middle third of the right shaft of the tibia - Distal right fibular shaft	Conservative management	Regressed in 5 months into a tiny intracortical lytic lesion in the tibia at age of 4 years	No	–
Smith et al. (Smith et al., 1991)	Newborn	Male	Proximal third of the right tibia	Conservative management	Regressed 12 months after diagnosis.	No	2.0 × 0.8 × 0.3
Anderson et al. (Anderson et al., 1993)	Newborn	Not specified	Proximal third of the anterior left tibia	Conservative immobilization by above-the-knee cast for eight weeks	Remodeling into normal anatomical bone appearance and density at age of 7 months.	No	–
Hindman et al. (Hindman et al., 1996)	4 weeks old	Male	Middle third of the anterior left tibia	No surgical intervention	The bone lesion has remained stable over the following 2-year period	No	3 × 2
Hindman et al. (Hindman et al., 1996)	17 days old	Male	Distal third of the right tibia and fibula	No surgical intervention	Incomplete healing occurred during a 3-month interval	Yes	–
Sunkara et al. (Sunkara et al., 1997)	4 weeks old	Female	Bilateral proximal anterior third of tibias	- Resection of left tibial lesion with allograft replacement - No intervention in the right lesion	In 2 years follow up: - Failure of healing of the left side - Intact right side	Yes (left side)	–
Sarisozen et al. (Sarisozen et al., 2005)	3 days old	Female	Proximal third of the anterior right tibia	No surgical intervention	Smaller lesion with persistent bowing in size at age of 4 years	No	–
Karol et al. (Karol et al., 2005)	5 weeks old	Male	Bilateral middle third of the anterior tibias	Long leg orthosis for 2 years	Right distal fibula fracture secondary to trauma at age of 7 years	No	–
Teo et al. (Teo et al., 2007)	At birth	Male	Entire left tibial shaft associated with pseudoarthrosis	Supramalleolar osteotomy of the tibia Physeal distraction and length correction	Initially angulation with 6-cm leg length discrepancy. No progression and doing well	Yes	–
Zamzam (Zamzam, 2008)	At birth	Male	Right tibia associated with pseudoarthrosis of the ipsilateral fibula	Curettage	Good functional recovery at 7 years of age	No	–
Çetinkaya et al. (Çetinkaya et al., 2012)	3 days old	Male	Proximal third of the anterior aspect of the right tibia	Conservative management, plaster-cast immobilization	Able to walk without limping	Yes	4 × 3
Jobke et al. (Jobke et al., 2014)	7 days old	Female	Central proximal dia-metaphysis of the left tibia	Biopsy followed by observation only.	Regression and normal development at 9-month follow up.	No	–
Sang Hoon Lee, (Kim and Lee, 2015)	7 days old	Female	Cortex and medullary of the right tibial meta-diaphysis right tibia and distal fibula.	No surgical intervention-incisional biopsy only.	Bowing deformity of the proximal tibia 3 weeks later and pathological fractures	Yes	–

with reconstruction. The recurrence rate was 35 % and was exclusively seen in the curettage group and reached statistical significance when compared with the excision group. The age of the patient at the time of the curettage was inversely proportional to rate of recurrence. The study did not show correlation between the age at initial presentation, lesion size, radiologic feature or history of fracture, and disease outcome (Park et al., 2018). Our case and other reported neonatal OFDs behaved similarly and none have reoccurred (Table 2).

4. Conclusion

OFD is a benign pediatric bone neoplasm that exclusively affects the tibia and/or fibula with overall favorable outcome. Here, we reported a rare neonatal OFD presentation with novel DDR2 and CDK12 gene mutations. Genetic interrogation of additional OFD cases is needed to explore the prevalence of these genetic aberrations, study their role in disease pathogenesis, if any, and their possible clinical utility.

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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.

Data availability

Data will be made available on request.

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