

Frontometaphyseal dysplasia 2 associated with thoracic deformity, and pulmonary arterial hypertension: a case report and review of literature

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ABSTRACT

Frontometaphyseal dysplasia 2 (FMD2) is a rare disease caused by *MAP3K7* gene mutation. We report a 7-year-old sporadic patient with FMD2 due to a de novo splicing variant in *MAP3K7*. He has the common characteristics of FMD2 but also has some characteristics that have never been reported, which increases the clinical phenotype of FMD2. Moreover, no systematic description of the imaging characteristics of FMD2 in computed tomography (CT) is available. In the present work, we found some different features of FMD2, reviewed previous literature, and summarized the general imaging manifestations of FMD2. This case emphasizes the important clinical value of CT and VR in the diagnosis of FMD2. We can clearly find the characteristics of FMD2 by CT examination, indicating its great significance for the prompt diagnosis and treatment of FMD2 patients.

Key words: *MAP3K7, diagnostic imaging, frontometaphyseal dysplasia 2, tomography, volume rendering imaging.*

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INTRODUCTION

Frontometaphyseal dysplasia 2 (FMD2) is characterized by skeletal features such as supraorbital hyperostosis, skeletal deformity, and joint contractures; patients with FMD2 tend to be deaf and have scoliosis, cervical fusions, and cleft palate.¹ FMD can be divided into two types. FMD1 is caused by mutations in *FLAN*, whereas FMD2 is caused by mutations in *MAP3K7*.² The FMD1 caused by *FLNA* mutations might be mediated by misregulation of signaling coordinated through the activated kinase (TAK1) signaling complex.³ *MAP3K7* encoding TAK1, and the mutations increase TAK1 autophosphorylation and alter the activity of signaling pathway regulated by the TAK1 kinase complex.² Less than 10 patients with FMD2 and *MAP3K7* mutations have been described thus far. Herein, we describe a 7-year-old boy with FMD2 caused by recurrent c.1454C>T *MAP3K7* mutation, which was identified as a de novo variant by whole-genome sequencing. The patient has the characteristic skeletal and facial features of FMD2. However, some novel features were also observed. Traditionally, the diagnosis of FMD2 is mainly based on gene diagnosis. To date, no systematic description of the imaging characteristics of FMD2 in computed tomography (CT) is available. FMD2 is rare in clinical practice. In this work, we reviewed previous literature and summarized the clinical and imaging features of the disease.

CASE PRESENTATION

A 7-year-old boy had cough that persisted for more than 20 days without improvement. His family brought him to our hospital for treatment. The cough was non-spasmodic and aggravated at night and after activity. Treatment with ceftizoxime and azithromycin was ineffective. He had no known significant medical history. He denied tobacco or alcohol use. No hereditary disease was noted in the family. No medication was taken before his hospitalization. He is the first child of the family and was born at the end

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of 2012. No abortion history was related for his mother. He is the only case in the family. There were no similar patients in his family and no related genetic history.

Upon physical examination, his pulse was 87 beats per minute, his blood pressure was 95/67 mmHg, and his respiratory rate was 16 breaths per minute. We observed that the patient had prominent supraorbital ridges; downslanting palpebral fissures; hypertelorism; broad nasal bridge; and abnormal shape of the hands, feet, right tibia, elbow, and knee (*Figure 1*).

The results of X-ray examination were as follows: metacarpal deformity of both hands; slight bending and thickening of the metaphysis of bilateral phalanges; incomplete fusion of partial phalanges of both thumbs; abnormality of bilateral phalanges, partial phalanges, and right distal tibia; pulmonary inflammation; and azygos lobe (*Figures 2.1-2.5*). Echocardiography revealed pulmonary hypertension, bicuspid aortic valve malformation, and mild tricuspid regurgitation. CT examination and volume rendering (VR) were performed. The results showed supraorbital hyperostosis, broad nasal bridge, azygos lobe, thoracic deformity, pulmonary inflammation change, deformity of hands and feet, bilateral knee joint and wrist joint shape abnormality, and pulmonary hypertension (*Figures 3 and 4*).

These findings were highly suggestive of FMD. To confirm the diagnosis, a gene test was conducted for the patient. The exon region and flanking intron region of 20,099 genes in the human exon group were detected by high-pass measurement sequence platform. The detection sequence data were compared with the hg19 reference sequence of the human genome, and the coverage and sequencing quality of the target region were evaluated. A group of heterozygous variation was found by gene detection: C.1535C>T(P.P512L) (OMIM: 617137 [GenBank: NM-145331.2]) (*Table 1*). The variation was consistent with that of HGMD and related to FMD2. Sanger sequencing confirmed that his parents had no such variation. Thus, the patient was diagnosed with FMD2.

With the clinical suspicion of FMD2 confirmed with genetic analysis, the patient and family were counseled and managed conservatively. During hospitalization, the treatment for the patient is mainly symptomatic therapies, such as use epocelin and azithromycin for anti-infective therapy; montelukast is used to decrease airway hyper-responsiveness; vitamin K1 is used to treat bleeding point in face. The patient was discharged from the hospital in stable condition. On outpatient follow up, the patient repeated episodes of bronchopneumonia. After timely

FIGURE 1. Prominent supraorbital ridges, downslanting palpebral fissures, broad nasal bridge and nasal tip could be observed on the face



and effective treatment, there were no serious complications, treatment was tolerated.

DISCUSSION AND CONCLUSIONS

We present a case with FMD2 due to *MAP3K7*

gene mutation. We made a detailed analysis about relevant publications, including our present case. FMD is a progressive disease of the bone and connective tissue.¹ Gorlin RJ et al., first reported the disease in 1969.⁴ There are two types

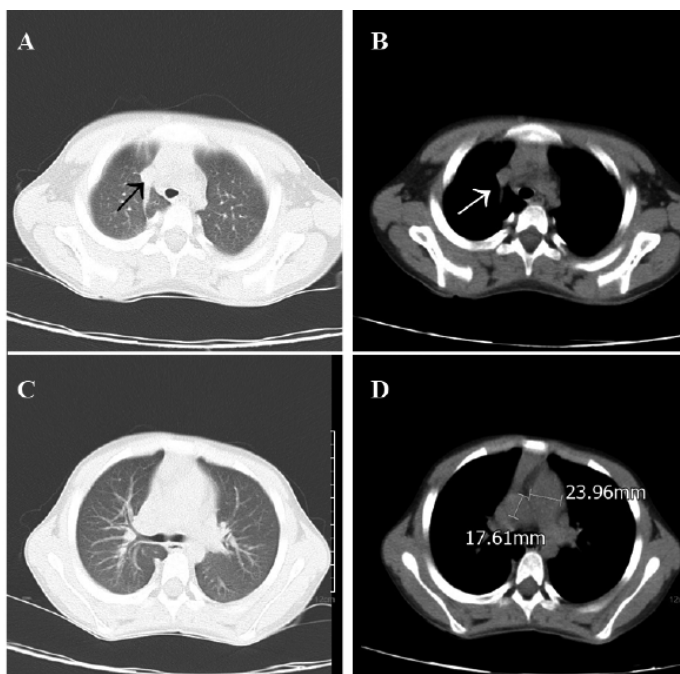
TABLE 1. The missense *MAP3K7* mutation

Gene	Genomic location	HGVS/cDNA	HGVS protein	Zygosity	Parent of origin	Variant interpretation
<i>MAP3K7</i>	Chr6:91228271 (GRCh37/hg19)	c.1535C>T/	p.P512L	Heterozygous	De novo	Pathogenic

FIGURES 2.1-2.5. Pulmonary inflammation; azygos lobe; slight curvature of the metacarpus; thickening of the metaphysis of bilateral phalanges; incomplete fusion of the partial phalanges of both thumbs; and abnormality of bilateral phalanges, partial phalanges, and right distal tibia



FIGURE 3. CT images of the patient: Shows the appearance of an azygos lobe to the right. Small patchy densities were seen in both lungs along the bronchovascular bundle. The diameter of the main pulmonary artery was 23.96 mm; The diameter of the ascending aorta was 17.61 mm; $23.96/17.61 = 1.36 (>1)$, The ratio was in accordance with the diagnostic criteria of pulmonary hypertension



of FMD:² FMD1 and FMD2. FMD1 is caused by mutations in the gene *FLAN*, whereas FMD2 is caused by *MAP3K7* mutation. In 2006, FMD was first reported caused without the *FLAN* mutation.⁵ Besse A, et al., prove that the missense mutation in *MAP3K7* would be causative of the FMD2.⁶ Wade et al. officially named FMD caused by *MAP3K7* mutation as FMD2 in 2016.² The clinical phenotype of FMD2 is similar to FMD1. In 2017, Emma M. Wade et al., gave a detailed description of the difference between FMD1 and FMD2.¹ Basart H et al., confirmed that there is a common pathological mechanism between *MAP3K7* and *FLAN* mutations, which will lead to the occurrence of FMD.⁷ Expanding the mutational spectrum of *MAP3K7*.⁷ A girl has the novel heterozygous c.737-7A>G variant in *MAP3K7* was reported in 2017.⁸ Growth retardation and spina bifida occulta as new features were reported, expands the clinical spectrum of FMD2.⁸ A novel missense mutation in *TAB2* associated with FMD was reported by Asuka Hori et al.⁹ A patient with cochlear implant was reported in 2021.¹⁰

In our case, we found the above typical manifestations of FMD2. However, some novel features were also observed, including azygos lobe, thoracic deformity, and pulmonary arterial hypertension. These findings increase the clinical phenotype of FMD2 and have important clinical value. Azygos lobe is a general change, which may only be a coincidence in our case. Thoracic deformity is the same type of bone system lesion as that reported in FMD2. Therefore, we conclude that thoracic deformity is the characteristic of FMD2. Masurel-Paulet A et al., reported the clinical phenotype of FMD1 patients with severe congenital lung disease in 2011, including pulmonary arterial hypertension.¹¹ Our case is the first report of pulmonary arterial hypertension as the clinical phenotype of FMD2. The report expands the clinical spectrum of FMD2.

At present, diagnosing FMD2 is still difficult, and whole-body gene test is usually the diagnostic standard. The diagnostic efficacy of radiological examination for FMD2 is improving by reviewing more cases of FMD2. Gene diagnosis

FIGURE 4. VR image of the boy: The patient's whole body skeleton can be observed clearly through VR image. Thoracic deformity and scoliosis can be observed. The patient's sternum protruded forward, which was consistent with the performance of pectus carinatum. The VR images show ulnar deviation of the hands and slightly curved of some phalanges and metatarsal. The elbow joint presented cubits valgus deformity, which was more severe on the right than on the left. A deformity of the knee joint can be clearly observed



also has limitations in FMD2. Compared with CT examination, gene diagnosis is more expensive and troublesome. To the best of our knowledge, this case is the first case that underwent whole-body CT scan and VR imaging. The imaging manifestations of FMD2 were described in detail to improve the diagnosis of FMD2.

First, we observed the typical characteristics of FMD2: prominent supraorbital ridges, downslanting palpebral fissures, hypertelorism, and broad nasal bridge. These features are common in FMD2. Second, the patient had thoracic deformity and scoliosis. Third, we observed changes of bilateral metacarpals: the shape of bilateral palmar accidents is abnormal and slightly curved, the epiphysis of bilateral finger diaphysis is thickened, a part of the phalanges of the bilateral thumbs is not fused, and morphological abnormality can be observed in the bilateral metatarsals and partial phalanges. The elbow joint presented cubitus valgus deformity, which was more severe on the right than on the left. We could clearly observe a deformity of the knee joint. The diameter of the pulmonary artery increased to 2 cm, suggesting that the patient has pulmonary hypertension. Finally, we found azygos lobe and cord shadow near the mediastinum of the right upper lung in the CT image. Through CT and VR images, we could observe the whole skeleton of the patient. At the same time, we could accurately judge the severity of these typical features and guide our clinical treatment. These findings are of great significance to the auxiliary diagnosis of FMD2. However, performing a whole CT on a child has limitations, connected to exposition to a huge quantity of unnecessary radiations. This case provides us with abundant image information, which has crucial clinical value.

In conclusion, we reported a case with some new features that add clinical phenotype of FMD2. This case is a good proof of the CT and volume rendering (VR) in the auxiliary diagnosis of FMD2. The characteristics of FMD 2 by CT examination were observed clearly. ■

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