Expansion of the clinical spectrum of frontometaphyseal dysplasia 2 caused by the recurrent mutation p.Pro485Leu in MAP3K7

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Abbreviations: FMD2: Frontometaphyseal dysplasia 2; MAP3K7: Mitogen-Activated Protein 3-Kinase 7; TAK1: Mitogen-Activated Protein Kinase 7; TGF-β: Transforming Growth Factor-β; NF-κB: Nuclear Factor-kappa B; BMP: Bone Morphogenetic Protein; FLNA: Filamin A; FMD1: Frontometaphyseal dysplasia 1; CDSCF: Cardiospondylocarpofacial syndrome

1. Introduction

Skeletal dysplasias constitute a large and heterogeneous group of disorders characterized by a broad phenotypic and genetic variability (Bonafe et al., 2015). Short stature is the main hallmark but many other features, including deformities and extra-skeletal manifestations, may also be present. Abnormalities in signaling pathways crucial for the growth plate, i.e. Notch, WNT, FGF, Hedgehog, and BMP pathways, are common causes of skeletal dysplasias (Geister and Camper, 2015).

Recently, heterozygous disease-causing mutations in MAP3K7, encoding the Mitogen-Activated Protein Kinase 7 (also known as TAK1), were described in Frontometaphyseal dysplasia 2 (FMD2) in less than 20 patients (Wade et al., 2016, 2017). This kinase is stimulated by TGF-β and BMPs and plays an important role in osteogenesis. Less than 20 patients with FMD2 and MAP3K7 mutations have been described thus far. The majority of the patients harbor a recurrent missense mutation, NM_003188.3: c.1454C > T [NP_003179.1: p.(Pro485Leu)], which leads to a more severe phenotype than mutations in other domains. Here we describe an additional patient with FMD2 caused by the recurrent c.1454C > T MAP3K7 mutation, identified as a de novo variant by whole-genome sequencing. The 17-year-old boy has the characteristic skeletal and facial features of FMD2. However, some novel features were also observed, including growth retardation and spina bifida occulta. In line with other patients harboring the same mutation he also showed keloid scars and had no intellectual disability. This report expands the clinical spectrum of FMD2 caused by the recurrent c.1454C > T (p.(Pro485Leu)) mutation in MAP3K7.

References


https://doi.org/10.1016/j.ejmg.2018.04.004

Received 12 January 2018; Received in revised form 14 March 2018; Accepted 10 April 2018
Available online 14 April 2018

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2. Clinical report

2.1. Clinical manifestations

The index patient and his healthy parents were recruited at the Folkhälsan Department of Medical Genetics to a research project exploring genetic causes of skeletal dysplasia. The study protocol was approved by the Research Ethics Board at Helsinki University Hospital and informed consents were obtained from the participants prior to the study.

The patient, a boy born to non-consanguineous Finnish parents, presented at birth with tetralogy of Fallot, a clavicular fracture, ulnar deviation of the wrists, contractures of the elbows, pes metatarsovarus, and hydronephrosis due to ureteral reflux (Table 1). The skull was somewhat dolichocephalic with a sloping forehead, the fontanelle was large, and vertebrae C3 and C4 had reduced height. The fingers and toes were long, with broad distal phalanges of the fingers. His birth weight, length and head circumference (3680 g/51 cm/35.5 cm) were normal, and he received 9 Apgar points.

His slight dysmorphic features included hypertelorism, down-slanting palpebral fissures, broad nasal root, full cheeks, grooved philtrum, small mouth, a H-shaped impression in the chin, and single palmar creases and camptodactyly in both hands. Hemangiomas were present on the forehead and the occiput and neck. He was treated with von Rosen’s cast for hip dysplasia and joint contractures and underwent corrective cardiac surgery at the age of 6 months.

On examination at age 1 year, in addition to the above-mentioned dysmorphic features, he was noted to have colobomas of the nostrils. Freeman-Sheldon syndrome was suspected. At the age of 3 years, he was observed to have a submucosal cleft palate and a hearing deficit requiring hearing aids.

At 6 years, the boy was found to have a craniocervical malformation (a sharp angle between the clivus and the dens, and caudal displacement of the conus) in combination with Chiari I malformation. He underwent occipito-cervical fusion to stabilize his neck (Fig. 1). Decompression of the foramen magnum was performed during the same operation because of the Chiari I malformation. He was found to have spina bifida occulta in several vertebrae and bilateral Sprengel deformities. The Halo bracing, used for stabilization, caused severe keloid formation in his back (Fig. 1D). He also underwent surgery for unilateral cryptorchidism. His orbital ridges were increasingly prominent (Fig. 1A–B) and a corrective surgery was performed at 11 years to flatten the protruding bony parts of the forehead.

The patient had always been sensitive to light but initial
examinations revealed no etiology. At the age of 6, he was found to have subepithelial corneal scarring (leucoma corneae), astigmatism, and amblyopia. At 7 years, he had short stature (−1.5 SD; Supplemental Fig. S1), scoliosis (Fig. 1C), slightly weak voice, and mild atopy, and was prone to infections. Intellectual development and school performance were normal.

His growth, which decelerated already starting from 3 to 4 years of age when scoliosis was not present, has progressed slowly despite normal pubertal development (Supplemental Fig. S1). By age 17 years, his scoliosis has significantly progressed (Cobb’s angle 42°) and may significantly progressed (Cobb’s angle 42°) and may have led to infections. Intellectual development and school performance were normal.

His growth, which decelerated already starting from 3 to 4 years of age when scoliosis was not present, has progressed slowly despite normal pubertal development (Supplemental Fig. S1). By age 17 years, his scoliosis has significantly progressed (Cobb’s angle 42°) and may partly explain the lack of pubertal growth spur and his severe height deficit (148 cm; −4.3 SDS). He has flexion contractures in the knees, hips and elbows and his feet are deformed and rigid.

2.2. Genetic findings

In order to identify the genetic cause in our index patient, we performed whole-genome sequencing (WGS) on the trio. Pair-end sequencing (2 × 150 bp) was performed at the SciLifeLab (Stockholm) on the HiSeqX instrument (Illumina), with an average coverage of 30 ×. Read alignment to the human genome assembly (GRCh37) was performed with the Burrow-Wheeler Aligner (BWA); data processing and variant calling were carried out using Genome Analysis Toolkit (GATK). Variants were annotated using Variant Effect Predictor (VEP) and data analysed using GEMINI. Candidate gene variants were filtered using a MAF < 0.001 in GnomAD and SweGen databases and assuming autosomal recessive/compound heterozygous inheritance pattern or a de novo variant (Ameur et al., 2017). Furthermore, we chose the impact severity of the variant to be different than “low” in GEMINI. Findings were validated by Sanger sequencing.

Whole-genome sequencing in our trio led to the identification of two heterozygous candidate genetic variants in the index patient, both identified as de novo: 1) a recurrent missense variant NM_003179.1: c.1454C > T [p.(Pro485Leu)] in MAP3K7 (Supplemental Fig. S2A and 2) a novel missense variant NM_020120.3: c.152C > T [p.(Leu51Pro)] in UGGT1, encoding the UDP-Glucose Glycoprotein Glucosyltransferase 1. UGGT1 is involved in the quality control of protein folding in the endoplasmic reticulum (Arnold et al., 2000). However, mutations in this gene have not been associated with any disease yet. On the other hand, mutations in MAP3K7 have been described in two skeletal diseases: FMD2 and cardio-pulmonary-gastrointestinal syndrome. Based on previous studies and phenotypic correlations, the variant in MAP3K7 was regarded as the cause of our patient’s disorder, confirming a diagnosis of FMD2. This finding, which was also validated with Sanger sequencing (Supplemental Fig. S2B-S2D), allowed us to re-evaluate our patient’s clinical features and compare with previously reported patients with the same recurrent p. (Pro485Leu) mutation in MAP3K7. 3. Discussion

Our patient had many features in common with the previously reported patients, including prominent supraorbital ridges, hypertelorism, down-slanting palpebral fissures, broad nasal bridge, full cheeks, micrognathia, hydronephrosis, cleft palate, hearing loss, scoliosis, ulnar deviation of the hands, campodactyly, wrist contractures, long fingers, structural cardiac defect and keloid scars (Table 1, Fig. 1) (Basart et al., 2015; Morava et al., 2003; Wade et al., 2016, 2017). Radiologically, he had a craniocervical malformation, Chiari I malformation, Sprengel deformity, spina bifida occulta, single palmar creases, pes cavus, and amblyopia. Amblyopia is common in the general population and it might be a coincidental finding in our patient. Furthermore, Chiari I malformation, Sprengel deformity and single palmar creases are similar to contractures and skeletal deformities described in other individuals with FMD (Basart et al., 2015; Robertson et al., 2003; Wade et al., 2016, 2017). In line with this, spina bifida occulta is part of the cervical spine dysraphism in FMD but it has never been reported hitherto in patients with MAP3K7 mutations. Finally, leucoma corneae and astigmatism were observed previously in one patient with a MAP3K7 mutation (Basart et al., 2015), suggesting that this feature may be a part of the phenotypic spectrum of FMD2.

The majority of the patients hitherto reported as having FMD2 harbor the same recurrent mutation as the one identified in our patient, c.1454C > T [p.(Pro485Leu)]. This mutation affects the TAB2 domain of the protein (Table 1; Supplemental Fig.S3) (Wade et al., 2016, 2017). Only 3 patients have been described as having other missense mutations (Wade et al., 2016, 2017). These mutations cluster closer to the N-terminal, in the tyrosine kinase domain, and give rise to milder phenotypes than the ones caused by the recurrent mutation (Table 1; Supplemental Fig. S3). Although the majority of features in our patient
overlap with the ones previously described in other FMD2 patients, his phenotype also includes some novel features (Table 1). For example, short stature has not been previously reported in FMD2. However, short stature is one of the hallmarks of patients with cardiospondylofaciofacial syndrome, which is also caused by MAP3K7 mutations (Le Goiff et al., 2016). Furthermore, our patient has additional hand and foot deformities as well as spina bifida occulta, vision problems, undescended testis and hemangiomas that have not previously been described in other patients with FMD2.

In summary, our detailed report corroborates many of the clinical features previously described in patients with FMD2 caused by the recurrent MAP3K7 mutation c.1454C > T [p.(Pro485Leu)] but also describes some novel or unusual characteristics, in particular growth retardation, which may suggest a partial overlap between FMD2 and cardiospondylofaciofacial syndrome.

Conflicts of interest

Alice Costantini, Carina Wallgren-Pettersson and Outt Mäkitie declare no conflict of interest.

Acknowledgments

The authors thank the Sigrid Jusélius Foundation, the Association Française contre les Myopathies, the Finska Läkaresällskapet, the Folkhälsan Institute of Genetics, the Medicinska understödsföreningen Liv och Hälsa, the Academy of Finland, the Swedish Research Foundation, the Novo Nordisk Foundation and Stockholm County Council (ALF) for funding. The authors would also like to acknowledge support from the National Genomics Infrastructure, NGI, and UPPMAX for providing assistance in massive parallel sequence analysis.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2018.04.004.

References


Web resources


GATK: https://software.broadinstitute.org/gatk/.


SweGen: https://swefreq.nbis.se.