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SHORT COMMUNICATION

Novel homozygous *TSFM* pathogenic variant associated with encephalocardiomyopathy with sensorineural hearing loss and peculiar neuroradiologic findings

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Abstract

TSFM is a nuclear gene encoding the elongation factor Ts (EFTs), an essential component of mitochondrial translational machinery. Impaired mitochondrial translation is responsible for neurodegenerative disorders characterized by multiple respiratory chain complex defects, multisystemic involvement, and neuroradiological features of Leigh-like syndrome. With the use of a next-generation sequencing (NGS)–based multigene panel for mitochondrial disorders, we identified the novel *TSFM* homozygous variant c.547G>A (p.Gly183Ser) in a 5-year-old boy with infantile early onset encephalocardiomyopathy, sensorineural hearing loss, and peculiar partially reversible neuroimaging features. Our findings expand the phenotypic spectrum of *TSFM*-related encephalopathy, offering new insights into the natural history of brain involvement and suggesting that *TSFM* should be investigated in pediatric mitochondrial disorders with distinctive neurologic and cardiac involvement.

Keywords Mitochondrial disease · Neuroimaging · Elongation factor · Leigh syndrome

Introduction

The mitochondrial double-stranded DNA (mtDNA) encodes 13 polypeptides involved in the oxidative phosphorylation (OXPHOS) system, which represents the primary source of cellular energy [1]. Mitochondrial translation depends on the concerted action of several translational factors and ribosomal proteins encoded by nuclear genes [2]. Impairments in this process are responsible of a subgroup of mitochondrial disorders with respiratory chain complex defects and multisystemic involvement [2]. In particular, the elongation factor Ts (EFTs) encoded by the nuclear gene *TSFM* (OMIM entry 604723) plays a pivotal role in the translation of mtDNA-encoded proteins [2, 3]. EFTs acts as a nucleotide exchange factor for EFTu, a G protein which is necessary for the guanosine triphosphate–dependent binding of amino-acylated tRNAs to the A-site of mitochondrial ribosomes [2, 3]. *TSFM* pathogenic variants cause a complex disorder falling within the spectrum of Leigh-like syndromes and characterized by predominant neurologic and cardiac involvement. Interestingly, susceptibility to multiple sclerosis has also been associated with an alternative *TSFM* transcript [4]. We describe a patient carrying a novel homozygous mutation in *TSFM* and presenting

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with early onset encephalocardiomyopathy with lactic acidosis, sensorineural hearing loss, and peculiar reversible brain lesions.

Patients and methods

Tissue and blood samples were obtained for diagnostic purposes after ethical approval from the Ethic Committee of our Institution and written informed consent from the patient's mother.

Muscle biopsy

Routine morphology and histochemical stains for oxidative metabolism in skeletal muscle biopsy were performed according to standard protocols.

Neuroimaging

Brain MRI studies were performed on 1.5 T and 3 T scanners with different protocols, but all included 3DT1-weighted, 3-mm-thick axial and coronal T2-weighted, axial FLAIR, and diffusion-weighted imaging sequences.

Genetic studies

Using the multigene panel *Mito Chip*, we studied by massive parallel sequencing the coding exons and 50 bp of flanking introns of 257 genes associated with mitochondrial disorders (list of genes available on request). Sanger sequencing was used for confirmation and segregation of the identified *TSFM* variant (RefSeq NM_001172696). RNA extracted from skin fibroblasts was reverse-transcribed into cDNA using Transcriptor First Strand cDNA Synthesis kit (Roche, Germany). cDNA was subsequently amplified by PCR using the following primers: TSFM_cDNA-F: 5′-CAGG AAGGAAACACAACTGTATTA-3′ and TSFM_cDNA-R: 5′-TAATAATTTTACCCATGCATTCTC-3′. Then, PCR products were loaded on a 2.5% agarose gel stained with ethidium bromide; the bands excised from gel using MinElute Gel Extraction Kit (Qiagen, Germany), and thereafter analyzed by Sanger sequencing.

Results

Case report

An 11-month-old boy was evaluated for diffuse hypotonia and developmental delay (DD). He was the only son of unrelated Italian parents. Family history was substantially unremarkable. Pregnancy and delivery were uncomplicated. Neonatal course was uneventful. At the age of 3 months, severe lactic acidosis and dehydration occurred during a bronchiolitis episode. In the following 3 months, he developed failure to thrive and hypotonia.

At the age 11 months, his weight was 6.6 kg (− 3.4 SD) and length 70 cm (− 1.47 SD). Neurological examination showed inconstant visual fixation and pursuits, generalized hypotonia with partial head control, supported only sitting position with kyphosis, and reduced muscle mass. Additional findings included epicanthal folds and a soft 2/6 mesocardial murmur. Blood tests revealed normal CK levels, elevation in lactate levels (42.7 mg/dl, range 8–22 mg/dl), hypobicarbonatemia (14.1 mEq/l, range 20–25 mEq/l) with increased anion gap (AG 20 mEq/l, range 8–16 mEq/l), and normal serum pH. Electroencephalogram was normal. Electrocardiogram revealed diffuse high voltage and diffuse ventricular repolarization alterations combined with small inferolateral Q waves, consistent with ventricular hypertrophy (Supplementary Fig. 1). Ultrasound examination showed a diffuse non-hemodynamically significant left ventricular hypertrophy with predominant septal involvement, suggestive of hypertrophic cardiomyopathy (HCM). Supplementation therapy with multivitamins (B1, B2, B6, B7, and coenzyme Q10) and oral sodium bicarbonate was started. Echocardiographic follow-up showed mild progression of the ventricular hypertrophy, which extended to the left ventricular anterolateral wall, and slight right ventricle involvement. No progression of neuromuscular symptoms was observed.

Physical examination at the age of 5 years showed persistent generalized hypotonia, broad-based gait, upper limbs dysmetria, generalized hyperreflexia, and severe speech delay (he was only able to speak few words). Blood tests showed normal CK levels with normal lactate (16 mg/dl) and persistent hypobicarbonatemia (16.4 mEq/l) with normal serum pH. Nerve conduction studies resulted negative. Ophthalmologic evaluation did not reveal any abnormality. At the age of 8 years, brainstem auditory evoked potentials showed the absence of V wave bilaterally at a threshold of 90 dB with both click and tone burst stimuli, consistent with profound sensorineural hearing loss. Echocardiography showed a stable HCM.

Neuroimaging

Brain MRI at 11 months of age revealed nonspecific multifocal confluent signal changes in the frontal and parietal periventricular white matter (Fig. 1a). Follow-up brain MRI performed at 1.7 years of age revealed mild reduction of the parietal white matter alterations and increase of the signal changes in the frontal regions. Moreover, there were bilateral T2-hyperintense lesions with restricted

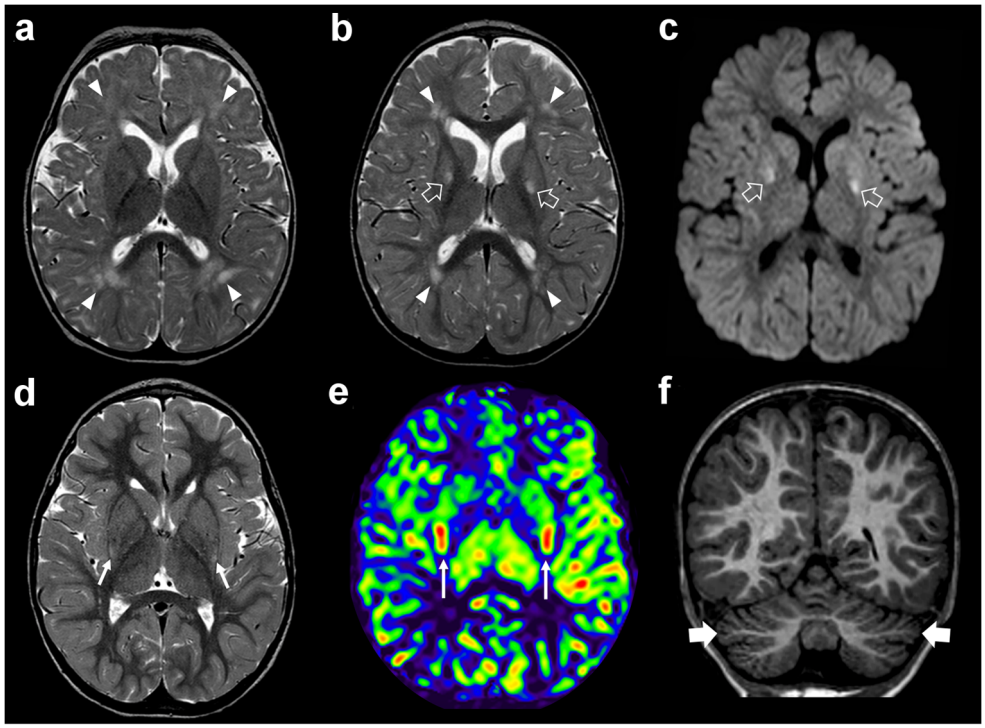

Fig. 1 Brain MRI scans at different ages. **a** Axial T2-weighted image at 10 months shows multifocal confluent periventricular white matter lesions in frontal, parietal, and occipital regions (arrowheads). **b** Axial T2-weighted and **c** diffusion-weighted images at 1.7 years reveal bilateral roundedT2-weighted hyperintensities with restricted diffusion in the medial portions of the putamina (empty arrows). The white matter lesions are reduced in the parietal regions and slightly increased in the frontal lobes (arrowheads). **d** Axial T2-weighted and corresponding color-coded ASL (**e**) images at 5 years of age demonstrate resolution of the white matter and medial putaminal lesions. There are new linear putaminal T2 hyperintensities with increased ASL signal (arrows). **f** Coronal reformatted 3D T1-weighted image reveals mild cerebellar atrophy (thick arrows)

diffusion in the medial portion of the putamen (Fig. 1b, c). At the age of 5 years, brain MRI showed complete resolution of the white matter lesions and medial putamina abnormalities. New small T2-hyperintense lesions with increased perfusion on arterial spin labeling (ASL) images were detected in the posterior portion of the putamina. Moreover, mild cerebellar atrophy was identified (Fig. 1d–f). Spectroscopy studies did not reveal an increase in lactate. Follow-up brain MRI scans at the age of 7 years showed a stable picture.

Muscle biopsy

Muscle biopsy revealed scattered red ragged fibers and some lipid vacuoles (Fig. 2). Histochemical studies showed a diffuse mild reduction of cytochrome C oxidase (COX) and increased succinate dehydrogenase (SDH) staining in few fibers (Fig. 2). Respiratory chain activities assay on muscle homogenates revealed a significant isolated reduction of both absolute COX activity (0.73 μmol/min/g tissue, range 1.80–2.45) and COX activity normalized to the activity of the matrix enzyme citrate synthase (0.068, range 0.140–0.250).

Genetic analysis

Analysis of the whole mtDNA in skeletal muscle and full sequencing of the coding exons of *SURF1*, *SCO2*, and *COX15* yielded negative results. Later, targeted next-generation sequencing (NGS) of a multigene panel for mitochondrial disorders using the MiSeq platform (Illumina, San Diego, CA) with probes designed by Agilent Sure Select system (Agilent Technologies, Santa Clara, CA) was performed. We identified the homozygous variant c.547G>A (p.Gly183Ser) in *TSFM* (NM_001172696, representing the longest transcript and encoding the longest isoform; NP_001166167), leading to the substitution of a highly conserved Glycine with a Serine. This variant was novel; it was not reported in the gnomAD polymorphic dataset (http://gnomad.broadinstitute.org/). When scored according to the guidelines from the American College of Medical Genetics and Genomics [5], the variant has a very strong prediction of pathogenicity (class 5). Noteworthy, this change affects the first nucleotide of exon 6 and creates a potential alteration of splicing (Human Splicing Finder: http://www.umd.be/HSF3/HSF.shtml). Accordingly, two transcripts were identified by *TSFM* cDNA expression analysis from dermal fibroblast, the

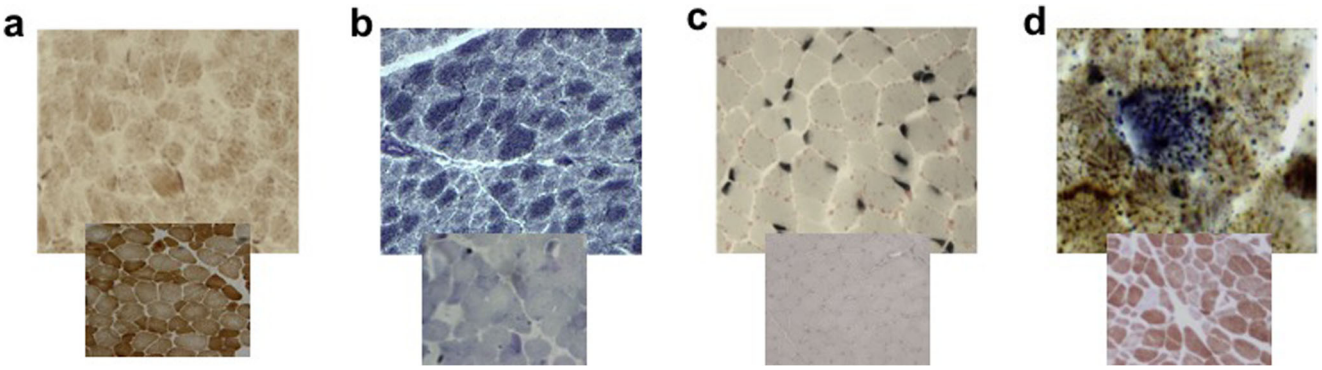

Fig. 2 Histopathological study findings. Upper panel shows example picture from patient, lower panel (smaller boxes) from a patient with normal results at each staining**. a** COX staining showing mild reduction of COX activity with some subsarcolemmal accumulation. **b** SDH staining demonstrating several fibers with increased SDH activity. **c** ORO staining reveal lipids accumulation (orange dots)**. d** Combined COX-SDH staining confirm that the COX-negative fibers stain blu for SDH

shorter lacked exon 6 (Fig. 3b), which is normally present in both the accepted transcript isoforms (Fig. 3c). The proband's mother was found to carry the heterozygous variant (Fig. 3a), whereas the father was not available for segregation analysis.

Discussion

TSFM-related encephalopathy falls in the spectrum of Leigh-like syndromes (Leigh syndrome OMIM entry 256000), a group of neurodegenerative disorders of mitochondrial energy generation characterized by heterogeneous etiology, episodic progression, and peculiar clinical and neuroradiological features [6]. Ophthalmologic involvement and multisystemic presentation are common in these conditions. Characteristics of neuroradiologic anomalies include bilateral symmetrical T2 high signal in the basal ganglia and brainstem, with restricted diffusion in the acute setting and occasionally elevated lactate on MR spectroscopy [6].

To date, *TSFM* mutations have been reported in 11 patients with a distinctive though variable phenotype including early onset encephalopathy and cardiomyopathy. Four out of the five described variants are located in exon 7 and affect the C-subdomain of the core domain, which plays a pivotal role in the interaction between EFTs and the domain III of EFTu [3, 7]. Variants in this subdomain have also been shown to alter the stability of EFTs and EFTs-EFTu complex, with negative impacts on translation [3, 8]. The only non-coding variant reported involves intron 2, probably resulting in abnormal *TSFM* expression or transcript instability [3]. Interestingly, our patient carried the first *TSFM* pathogenic variant located in exon 6 and affecting the N-subdomain of EFTs core domain. This subdomain is implicated in the interaction with the domain I of EFTu and promotes the guanine nucleotide exchange, a pivotal step in the elongation process of translation [2, 3, 7]. As a consequence, the c.547G>A (p.Gly183Ser) variant might impair the formation of the EFTs-EFTu complex and adversely affect EFTu function during elongation.

Common neurological findings in *TSFM* encephalocardiomyopathy include hypotonia, ataxia, dystonia, and tremors. Cardiac involvement is represented by early onset HCM. Myopathy is frequent and associated with decreased OXPHOS system function (Table 1). In line with previous reports, our patient presented with failure to thrive, severe DD, and early onset hypotonia. However, these symptoms occurred after an acute metabolic decompensation and did not significantly worsen over time. At the same time, his HCM was only slightly progressive in the initial stages and gradually stabilized. These findings suggest that acute metabolic decompensations might play a relevant role in the progression of *TSFM*-related encephalocardiomyopathy and that a thorough metabolic control by early sodium bicarbonate supplementation could be of paramount importance in these patients.

The vast majority of the previously reported patients showed variable signs of diffuse myopathy, including weakness, easy fatigability, and respiratory failure. Common findings included decreased COX stain on muscle biopsy and variable association of defects of OXPHOS complexes I, III, and IV (Table 1). Some individuals also showed peripheral neuropathy and optic neuropathy/atrophy [8, 9]. Despite our patient had normal peripheral nerve tests and ophthalmologic evaluations, he showed a severe bilateral sensorineural hearing loss. Of note, an adult-onset complex generalized hyperkinetic movement disorder with symmetric subthalamic T2-hyperintensities has been recently reported in a 20-year-old man carrying a homozygous missense mutation in *TSFM* [10]. According to these observations, it seems reasonable to speculate that the impaired mitochondrial protein synthesis in *TSFM*-related disorders might cause a diffuse though variable neuronal damage, leading to the typical heterogeneous expressivity of these conditions.

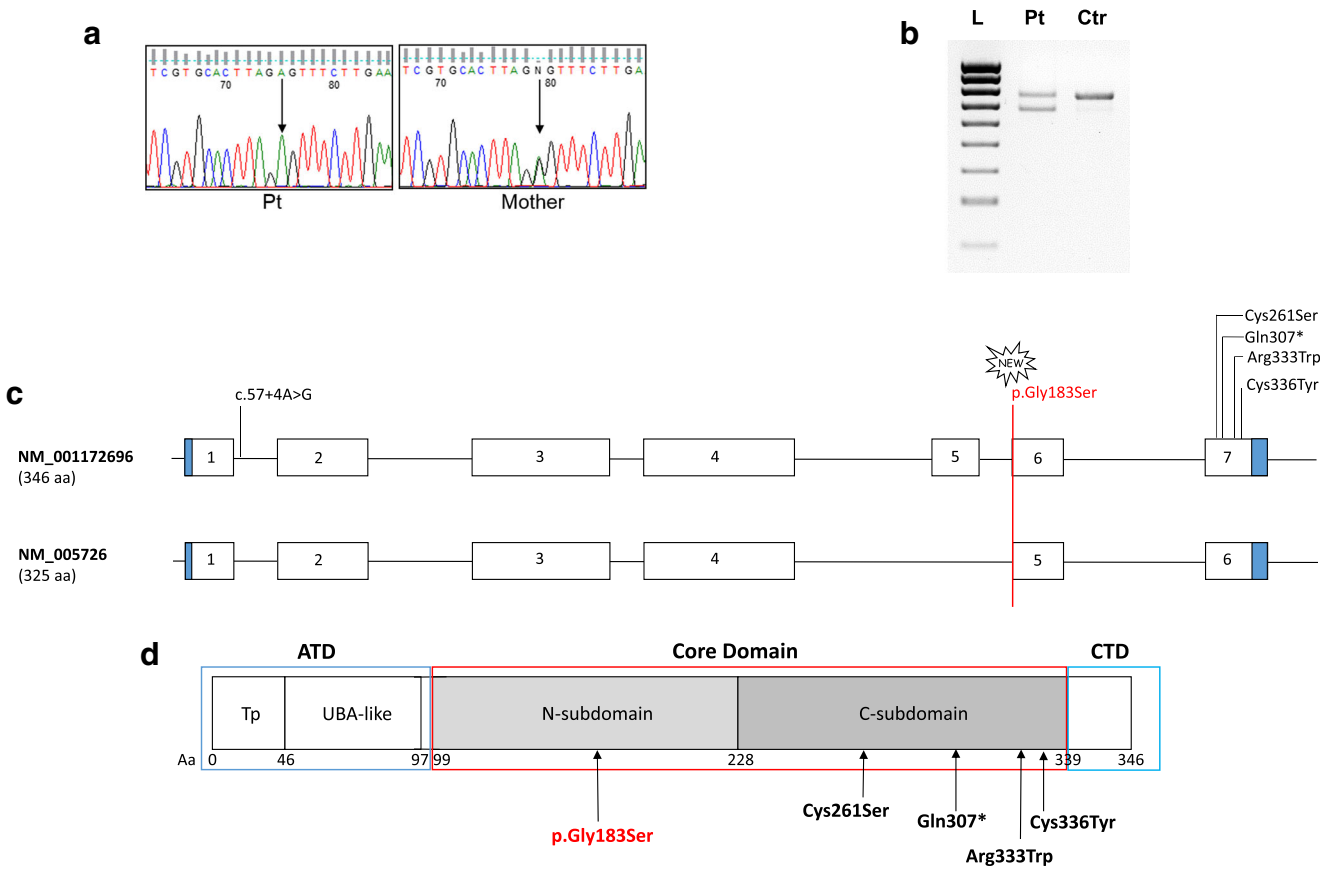

Fig. 3 Genetic findings. **a** Sequence chromatographs of *TSFM* region presenting the missense mutation c.547G>A (p.Gly183Ser), indicated by an arrow, in the affected patient (Pt) and his mother. **b** cDNA analysis on skin fibroblasts showing the formation of two transcript in the patient (Pt), the shorter one due to the skipping of exon 6. Sequencing of the normal sized transcript revealed the presence of the mutation in homozygosity. L, DNA size marker (100 bp); Ctr, control. **c** Schematic representation of *TSFM* gene structure showing the localization of all reported pathogenic variants. **d** EFTs protein structure (NP_001166167) and distribution of previously reported pathogenic variants. The N-terminal domain contains a transit peptide responsible for the translocation of nuclear-encoded protein to the mitochondria and an ubiquitin associated-like domain implicated in the interaction with EFTu. The core domain is the primary mediator of the dimerization with EFTu. Protein details available at https://www.ensembl.org (TSFM-201, transcript ID ENST00000323833), https://www.uniprot.org (ID P43897), https://www.ncbi.nlm.nih.gov/projects/CCDS/CcdsBrowse.cgi (ID CCDS53809). Aa, amino acid; ATD, amino-terminal domain; Tp, transit peptide; UBA-like, ubiquitin associated-like domain; CTD, carboxy-terminal domain

From the metabolic point of view, hyperlactatemia represents the most common finding, occurring sometimes in the context of a severe metabolic acidosis or very rarely associated with rhabdomyolisis (Table 1). Of note, Vedrenne et al. reported two individuals with early onset cholestasis and liver dysfunction that progressed to liver failure in one case [11]. As to the disease course, precocious death within the first 2 months of life has been reported in severely affected patients, whereas milder phenotypes are associated with longer survivals [8, 9, 11, 12]. A clear genotype-phenotype correlation is far from being established.

Remarkably, our patient showed a unique pattern of spontaneously regressing brain MRI lesions, never described in other individuals carrying *TSFM* pathogenic variants. Reversible brain lesions have been occasionally described in patients with metabolic disorders, including disorders of amino acid metabolism (such as phenylketonuria, cystathionine β-synthase deficiency, and maple syrup disease), Wilson's disease, and oxidative metabolism defects [6, 13–15]. In particular, the progressive involvement of different gray matter structures (i.e., globi pallidi, inferior olivary nuclei, dentate nuclei, and periaqueductal gray matter) during acute episodes, followed by almost complete reversibility in the intercurrent periods, has been reported in a patient with pyruvate dehydrogenase complex deficiency (PDHC) [13]. Similarly, our patient showed multifocal supratentorial white matter changes, occurring after a single episode of acute metabolic decompensation and gradually improving in the following months. At the same time, new lesions with cytotoxic edema appeared in the lenticular nuclei. Interestingly, these neuroimaging findings were not associated with any concurrent substantial change in the patient's clinical conditions. Follow-up MRI studies showed regression of these brain lesions, appearance of new persistent posterior putaminal changes with hyperperfusion on ASL images, and mild cerebellar atrophy. The

Table 1 Summary of the patients with *TSFM* pathogenic variants reported in the literature compared with our case

	Calvo et al., SciTranslMed, 2012	Calvo et al., SciTranslMed, 2012	Smeitink et al., Am J Hum Genet, 2006	Smeitink Am et al., J Hum Genet, 2006	Ahola S et al., Neurology, 2014 (P1, sister of P2)	Ahola S et al., Neurology, 2014 (P2, sister of P1)
Sex, age at onset	Pt1: M, < 1 week	Pt2: F, < 1 mo	Pt1: M, d1	Pt2: F, d2	Pt1: F, 10 mo (sister of Pt2)	Pt2: F, 16 mo (sister of Pt1)
Ethnicity; consanguinity	N/A; yes	N/A; yes	Turkish; yes	Kurdish Jewish; yes	Finnish; no	Finnish; no
TSFM mutations (RefSeq NM_001172696)	HOM c.997C>T (p.R333W)	HOM c.997C>T (p.R333W)	HOM c.997C>T (p.R333W)	HOM c.997C>T (p.R333W)	c.1007G>A (p.C336Y); c.919C>T (p.Q307*)	c.1007G>A (p.C336Y); c.919C>T (p.Q307*)
Neurologic	Hypotonia	Hypertonia	Hypotonia; generalized seizures	Apathy, irregular breathing, hypotonia	Cognitive decline (7 y); dystonic dyskinesia; ASMN	Mild learning difficulties; ASMN
Cardiac features (age of onset)	HCM	HCM	Normal septum thickness and contractility	Progressive concentric HCM	HCM (10 mo), stable on medications	HCM (16 mo), stable on medications
Other clinical features	FTT, hypothermia hepatomegaly	FTT, respiratory arrest	Respiratory failure	–	Fatigue and weakness; optic atrophy	Weakness; optic atrophy
Brain imaging	N/A	N/A	US: reduced gyri, plexus bleeding, and abnormal thalamic signal	Normal CT	MRI: normal at 3 y; bilateral T2-hyperintensity in putamen and globus pallidus at 9 y	Normal MRI at 11 y
Metabolic	N/A	N/A	Rhabdomyolysis, LAC (pH 6.8)	LAC (ph 6.9);↑ ammoniemia, ↑ketonemia	↑Serum and CSF lactate	↑Serum lactate
EMG	N/A	N/A	N/A	N/A	Polyphasic potentials	Mild myopathic changes
Muscle biopsy	N/A	N/A	N/A	Diffusely ↓COX stain, normal SDH stain	COX-negative fibers	Normalhistopathology
OXPHOS complexes activity	↓CI, CIII, and CIV	↓CI, CIII, and CIV	↓CI, CIII, and CIV	↓CI, CIII, and CIV	↓CI, CIII, and CIV	↓CIV
Peripheral nerve studies	N/A	N/A	N/A	N/A	ENG: ↓sensory amplitude and absent F-responses in lower limbs	ENG: ↓motor and sensory amplitude in lower limbs
Precocious death	2 mo	1 mo	7 we	10 we	No	No

	Ahola S et al., Neurology, 2014 (P3)	Emperador S et al., Eur J Hum Genet, 2017	Vedrenne et al., J Hepat, 2012	Vedrenne et al., J Hepat, 2012	Traschütz A et al., Parkinsonism Relat Disord, 2018	Our case
Sex, age at onset	M, 15 y	M, 6 y	Pt2: F, d1 (sister of Pt3)	Pt3: F, d1 (sister of Pt2)	M, 18 y	M, 3 mo
Ethnicity; consan-guinity	Finnish; no	Galician; no	Sub-Saharan; yes	Sub-Saharan; yes	Turkish; yes	Italian; no
TSFM mutations (RefSeq NM_	c.919C>T (p.Q307*); c.57+4A>G	HOM c.782G>C (p.C261S)	HOM c.997C>T (p.R333W)	HOM c.997C>T (p.R333W)	HOM c.1007G>A (p.C336Y)	HOM c.547G>A (p.G183S)

Table 1 (continued)

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Neurologic	Normal cognitive function; ASMN; tremor, ataxia	Lack of coordination, abnormal balance, dystonia, dysarthria	Hypotonia	Hypotonia, poor spontaneous movements, dystonia	DD; generalized chorea, myoclonic movements, dystonia, dysarthria, gait ataxia	DD; hypotonia; dysmetria; ataxia; hyperreflexia
Cardiac features (age of onset)	–	HCM (11 y), stable on medications	–	HCM	–	Progressive HCM
Other clinical features	Optic neuropathy	Optic atrophy	IUGR; tubulopathy; cholestasis; liver insufficiency	IUGR; cholestasis	Subclinical optic atrophy	FTT; low muscle mass; sensorineural hearing loss
Brain imaging	Normal MRI at 15 y	MRI: normal at 8 y; T2-hyperintensity in lenticular nuclei and right caudate nucleus at 14 y	N/A	N/A	Subthalamic T2-hyperintiensities	MRI: fronto-parieto-occipital WMLs(1 y); additional WMLs in lenticular nuclei (2 y); almost complete resolution of WMLs, initial cerebellar atrophy (5 y)
Metabolic	Normal serum lactate	Normal serum and CSF lactate	↑Serum lactate and AST	↑Serum lactate and AST	N/A	LAC during viral infection
EMG	Normal	Normal	N/A	N/A	N/A	N/A
Muscle biopsy	Atrophic type-II fibers, COX-deficient fibers	Red granular material (Gomori trichrome staining)	N/A	N/A	N/A	RRF with ↑lipid content; diffusely ↓ COX stain; sparsely ↑SDH stain
OXPHOS complexes activity	Normal	↓↓CI and CIV,↑CII	↓CI and CIV	↓CI and CIV	N/A	↓CIV
Peripheral nerve studies	ENG: ↓MNCV in lower limbs; ↓SNCV and amplitude in upper limbs; Nerve biopsy: demyelination, axon loss, and hypertrophy	ENG: ↓sensory amplitude and disintegration of somatosensory-evoked potentials in lower limbs	N/A	N/A	N/A	Normal ENG
Precocious death	No	No	2 mo	2 weeks	No	No

Abbreviations: *ASMN*, axonal sensorimotor neuropathy; *AST*, aspartate aminotransferase; *C*, complex; *COX*, cytochrome oxidase; *d*, day; *DD*, developmental delay; *EMG*, electromyography; *ENG*, electroneurography; *F*, female; *FTT*, failure to thrive; *HCM*, hypertrophic cardiomyopathy; *HOM*, homozygous; *LAC*, lactic acidosis; *M*, male; mo, months; *MNCV*, motor nerve conduction velocity; *MRI*, magnetic resonance imaging; *N/A*, not available; *OXPHOS*, the oxidative phosphorylation; *Pt*, patient; *RRF*, red ragged fibers; *SDH*, succinate dehydrogenase; *SNCV*, sensory nerve conduction velocity; *WMLs*, white matter lesions; *y*, years

behavior and distinctive appearance of these lesions on perfusion imaging might point towards altered autoregulatory mechanisms in endothelial and smooth muscle cells from impaired mitochondrial activity, and/or neuronal hyperexcitability similar to what reported in MELAS stroke-like episodes [16–18]. However, the exact pathogenesis of these alterations remains unknown.

In conclusion, we report a further patient with *TSFM*-related encephalocardiomyopathy and a peculiar phenotype characterized by sensorineural hearing loss and partially reversible brain lesions. Our findings widen the knowledge about the neuroradiologic alterations in this disorder and expand its phenotypic spectrum. Few patients have been reported so far and further studies are needed to confirm our observations. However, these findings support the idea that *TSFM*-encephalopathy behaves as a distinctive clinical and radiological entity, and suggest that *TSFM* should be considered in the differential diagnosis of pediatric mitochondrial disorders with severe neurologic and cardiac involvement.

Compliance with ethical standards

Tissue and blood samples were obtained for diagnostic purposes after ethical approval from the Ethic Committee of our Institution and written informed consent from the patient's mother.

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