

A Novel *FBXL4* Variant Presenting with Shunt-Dependent Hydrocephalus

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Abstract

FBXL4-associated encephalomyopathic mitochondrial depletion syndrome type 13 is a very rare mitochondrial disorder. To date, more than 110 cases have been reported in the literature, and the disease presents with multisystem involvement accompanied by lactic acidosis. We aimed to expand the phenotypic spectrum by reporting a case with a previously undescribed c.1390-2A>G variant in the *FBXL4* gene and a previously unreported clinical presentation of severe hydrocephalus. The patient presented with severe lactic acidosis, developmental delay, moderate hyperammonemia, hypotonia, dysmorphic features, seizures, intrauterine growth restriction, hypertrophic cardiomyopathy, severe hydrocephalus, peripapillary atrophy, and encephalopathy. We aimed to contribute to the literature by identifying a new splice-site variant and the severe clinical presentation associated with it, thereby expanding the phenotypic spectrum, and by deepening understanding of the genotype-phenotype relationship of splice-site mutations.

Keywords: *FBXL4* gene, Mitochondrial depletion syndromes, Lactic acidosis, Hydrocephalus

INTRODUCTION

Mitochondria are organelles involved in cellular energy production and apoptosis. Mitochondrial proteins are encoded by both nuclear and mitochondrial DNA. Most of these proteins are encoded by nuclear DNA, which is thought to contain between 1,000 and 1,500 genes. *F-box and leucine-rich repeat protein 4* (*FBXL4*) is a mitochondrial protein localized to the intermembrane space, encoded by the nuclear *FBXL4* (MIM#605654) gene, and is a member of the F-box protein family. The F-box portion of the protein interacts with the Skp1 adaptor to assemble the Skp1-Cullin1-F-box E3 ubiquitin ligase complex, which ubiquitinates the mitophagy receptors BNIP3 and NIX, leading to their degradation and suppression of mitophagy.¹⁻³

FBXL4-associated disease was first described in 2013. In these studies, it was noted that the *FBXL4* protein was localized between the inner and outer mitochondrial membranes, and that impairment of its function resulted in mtDNA depletion, mitochondrial structural abnormalities, and reduced activity of oxidative phosphorylation enzymes.^{2,3} Common clinical manifestations of the disease, defined as *FBXL4*-associated encephalomyopathic mitochondrial depletion syndrome type 13, include hypotonia, lactic acidosis, growth retardation, facial dysmorphism, malnutrition, and cerebral atrophy. Although less frequent, the following manifestations are also observed: microcephaly, hyperammonemia, nystagmus, strabismus, optic atrophy, cardiac involvement, and seizures.⁴ While hydrocephalus has previously been reported, no case of severe hydrocephalus necessitating ventriculoperitoneal (VP) shunt placement has been described to date.



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CASE REPORT

The patient, a 34-month-old boy, was born at term by cesarean section to a 36-year-old mother from a 1st cousin marriage. His four siblings do not have any health problems. Elevated lactate levels were detected at 6 months of age. Thiamine 100 mg/day, riboflavin 100 mg/day, coenzyme Q10 100 mg/day, biotin 10 mg/day, and sodium benzoate 250 mg/kg/day were started on suspicion of mitochondrial disease.

The patient’s body weight was 10 kg [standard deviation score (SDS)≤−3.0], height was 92 cm (SDS −1.88), and head circumference was 51 cm (SDS +0.28). He had growth retardation, developmental delay, hypotonia, and dysmorphic features. Dysmorphic features included a prominent forehead, a long, smooth philtrum, retrognathia, micrognathia, thick eyebrows, upslanting palpebrae, long eyelashes, and a thin upper lip (Figure 1).

Laboratory examination revealed a mild elevation of aspartate aminotransferase (116 U/L; maximum level of 225 U/L). The acylcarnitine profile was normal. Analysis of plasma amino acid levels revealed an elevated alanine concentration of 1302 μmol/L [reference range (RR): 157-481]. Urine organic acid analysis revealed elevated levels of pyruvic acid (108 Mmol/molcre; RR: 0-32), lactic acid (364 Mmol/molcre; RR: 0-60), 2-ketoglutaric acid (209 Mmol/molcre; RR: 0-136), 3-hydroxybutyric acid (108 Mmol/molcre; RR: 0-63), 3-hydroxyisobutyric acid (108 Mmol/molcre; RR: 0-28), and 2-hydroxybutyric acid (6.4 Mmol/molcre; RR: 0.03-1.8). Lactate levels ranged from 3.2 to 17.1 Mmol/L (RR: 0-2). Ammonia levels were between 57 and 243 mcg/dL (RR: 31-123). Eye examination revealed peripapillary atrophy, whereas echocardiography showed left ventricular hypertrophy.

Imaging performed at 3 months of age showed dilatation of both lateral ventricles (left, 25 mm; right, 23 mm) and mild dilatation of the 3rd and 4th ventricles. Because the diagnosis

remained unclear, the ventricular dilation identified on previous cranial magnetic resonance imaging (MRI) did not fully explain the clinical picture; hypotonia and developmental delay persisted, and lactic acidosis raised suspicion for an underlying mitochondrial disorder. A repeat cranial MRI was performed at 2 years and 10 months of age. Cranial MRI showed severe tetraventricular hydrocephalus. Bilateral cortical sulci were partially effaced. The corpus callosum was hypoplastic. Genetic analysis revealed a homozygous c.1390-2A>G variant in the *FBXL4* gene (rs1263785322) (Figure 2). The variant has not been reported in the homozygous state in gnomAD Exomes, 1000 Genomes, ESP6500, and ExAC databases. The variant was classified as likely pathogenic because it met the PVS1 and PM2 criteria of the ACMG variant classification.

The patient underwent VP shunting for hydrocephalus at the age of 39 months. A postoperative cranial computed tomography scan showed severely dilated ventricles and a VP shunt (Figure 3). Phenytoin was started preoperatively as prophylaxis. After the shunt operation, we admitted the patient because of malnutrition and metabolic acidosis. The patient received nasogastric tube feeding. Sodium alginate and pantoprazole were initiated for vomiting in a patient with *FBXL4*-associated encephalomyopathic mitochondrial depletion syndrome type 13. Electroencephalography performed at the 3rd postoperative month was compatible with both a highly active, multifocal epileptic disorder and cerebral dysfunction.



Figure 1. (a, b) Prominent forehead, long and smooth philtrum, micro-retrognathia, thick eyebrows, upslanting palpebra, long eyelashes, thin upper lip.

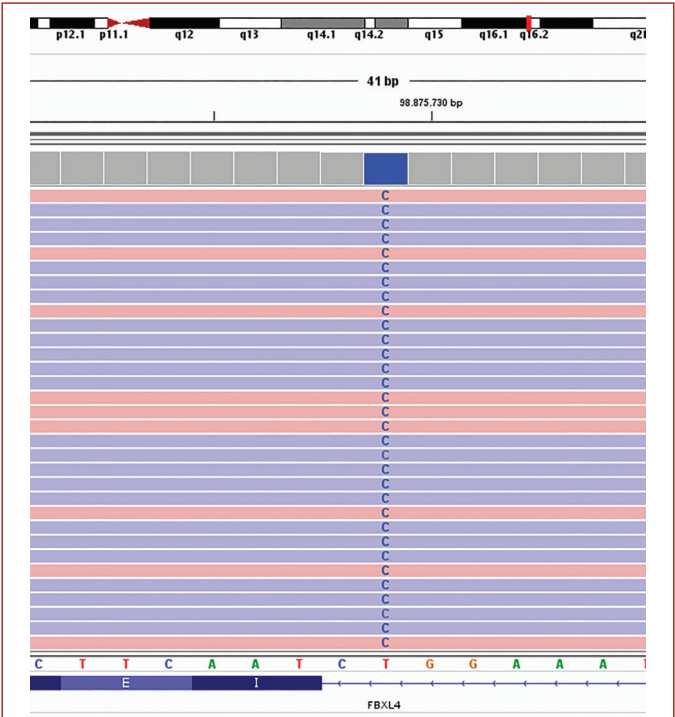
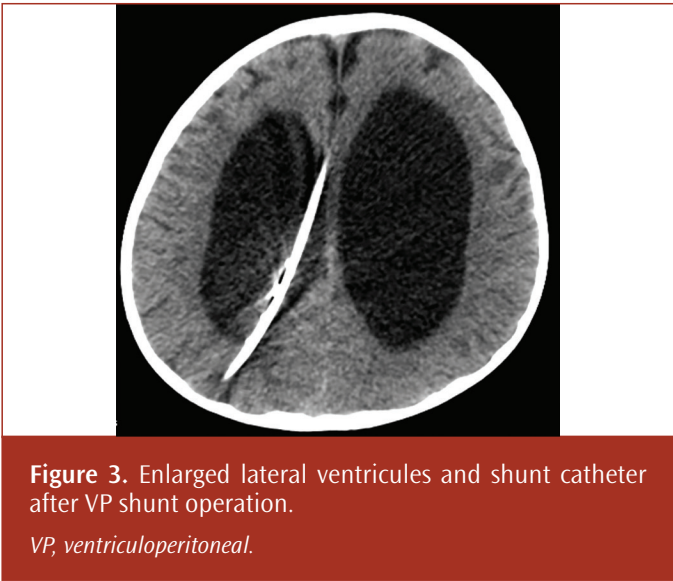


Figure 2. Integrative Genomics Viewer visualization of c.1390-2A>G variant.

MR spectroscopy performed at the 3rd postoperative month showed no lactate peak in a single-voxel view with a medium-length TE in the thalamic region of the deep gray matter; no peak was detected in other regions (Figure 4). MRI performed at 6 months postoperatively showed enlarged ventricles and diffuse, symmetric, mild signal enhancement in the thalamus, nucleus caudatus, and lentiformis on the T2 series (Figure 5). In the same imaging series, signal enhancement was observed in



the brainstem at the level of the middle cerebellar peduncles (Figure 6).

A cerebrospinal fluid culture performed because of encephalopathy revealed growth of vancomycin-sensitive *Staphylococcus epidermidis*. Appropriate antibiotic therapy was initiated. An external ventricular drain was placed, antibiotic therapy was initiated, and topiramate, levetiracetam, and clonazepam were added to the treatment regimen for seizures and dystonic contractions. Proteinuria was detected. Blood gas analysis revealed a pH of 6.89, a pCO₂ of 88 mmHg, an HCO₃ of 16.6 mg/dL, and a lactate of 14.5 Mmol/L; sodium dichloroacetate was administered at 50 mg/kg/day, and hemodialysis was therefore performed. He died of sepsis and encephalopathy at 45 months of age (Table 1).

Method

From the patient, 2 mL of peripheral blood was collected in EDTA tubes and stored at −20 °C. Genomic DNA was isolated from peripheral blood leukocytes using QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) according to the manufacturer’s protocols. All coding exons and exon-intron boundaries of 4493 genes were amplified using the Clinical Exome Solution v2 kit (SOPHiA Genetics, Boston, USA).

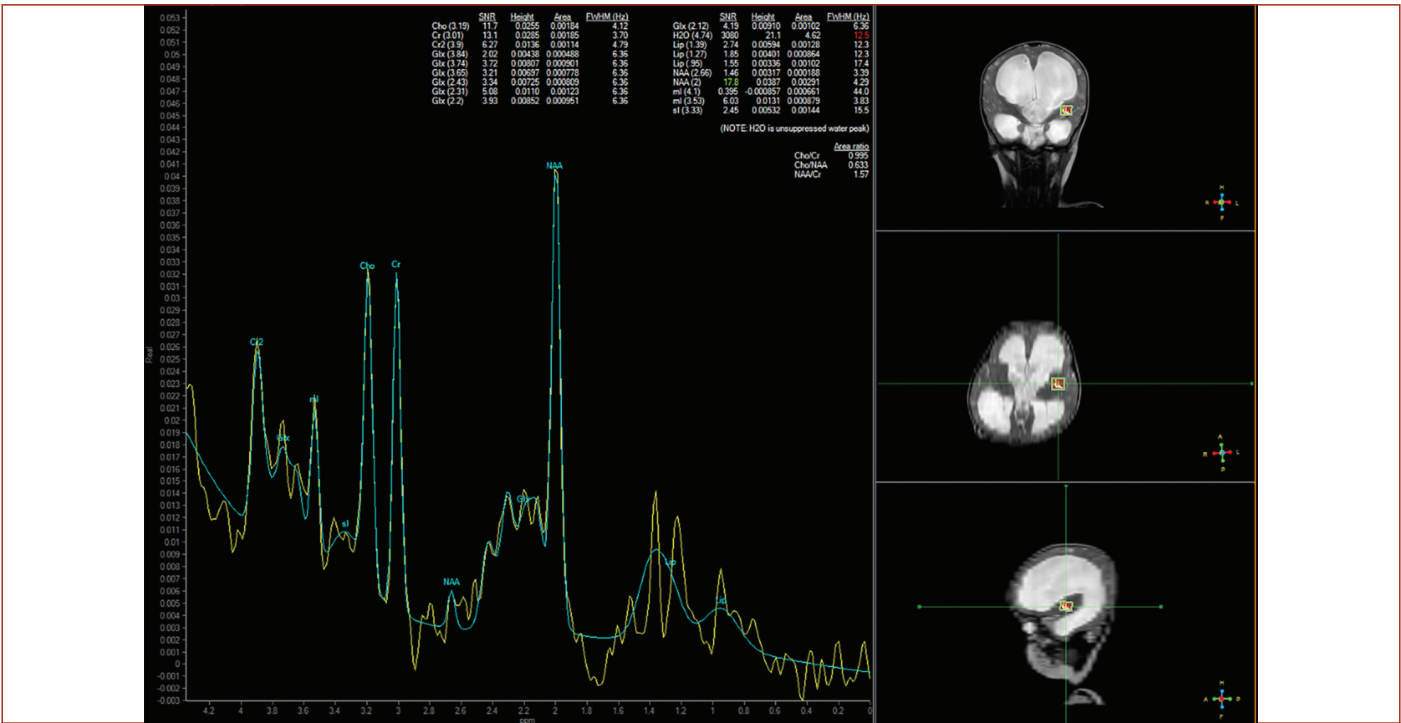


Figure 4. Brain MR spectroscopic imaging of the patient at the 3rd postoperative month revealed lactate peak on single-voxel MR spectroscopy with a medium-length TE in the thalamic region of the deep gray matter.
MR, magnetic resonance.

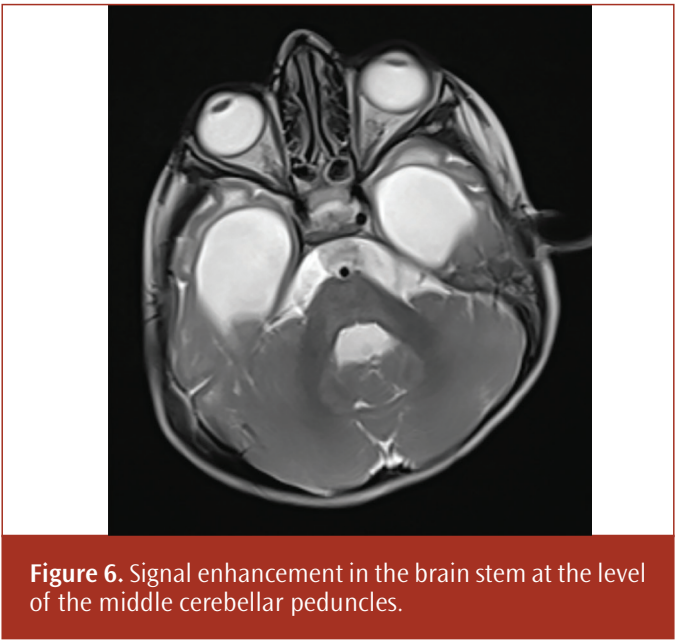
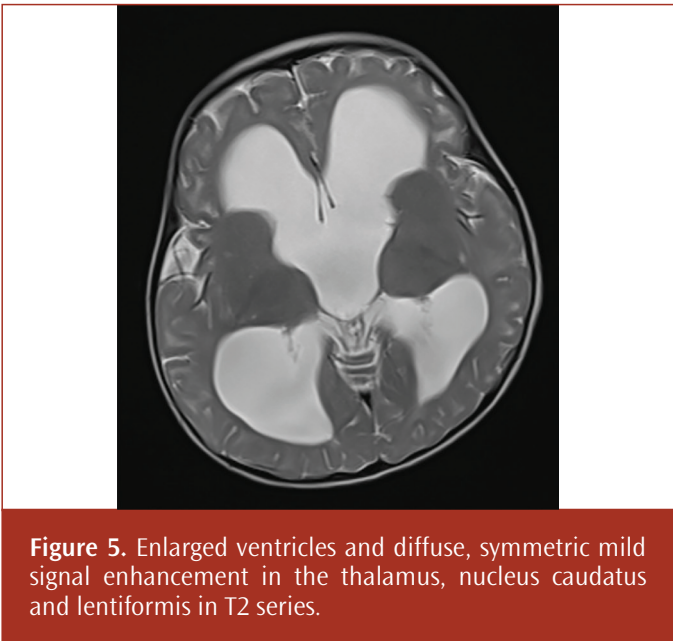


Table 1. Chronological timeline of the patient’s clinical course.		
Age	Clinical findings/investigations	Management
3 months	Cranial MRI: Dilatation of both lateral ventricles and mild dilatation of the third and fourth ventricles.	
6 months	Persistent hyperlactatemia and hyperammonemia detected; mitochondrial disease suspected.	Mitochondrial support and sodium benzoate treatment was initiated.
34 months	Growth retardation, developmental delay, hypotonia, dysmorphic features, persistent lactic acidosis, hyperalaninemia, intermittent hyperammonemia, peripapillary atrophy, and left ventricular hypertrophy. Repeat cranial MRI: severe tetraventricular hydrocephalus and hypoplasia of the corpus callosum. Genetic test: Homozygous <i>FBXL4</i> c.1390-2A>G likely pathogenic variant.	Metabolic investigations performed. Molecular diagnosis of <i>FBXL4</i> -associated encephalomyopathic mitochondrial DNA depletion syndrome established.
39 months	Progressive hydrocephalus.	Ventriculoperitoneal (VP) shunt placement; prophylactic phenytoin initiated.
42 months (3 months after VP shunt)	EEG showed highly active multifocal epileptic disorder with cerebral dysfunction. MR spectroscopy demonstrated a mild lipid-lactate peak in the bilateral thalami.	Antiepileptic treatment continued.
45 months (6 months after VP shunt)	Follow-up MRI showed persistent ventricular enlargement and new bilateral symmetric T2 hyperintensities involving the thalami, caudate nuclei, lentiform nuclei, and brainstem (middle cerebellar peduncles).	
45 months	Encephalopathy; CSF analysis: <i>Staphylococcus epidermidis</i> . Proteinuria, severe metabolic acidosis (pH 6.89, lactate 14.5 mmol/L), sepsis, seizures, and dystonic contractions developed.	External ventricular drainage, targeted antibiotic therapy, topiramate, levetiracetam, clonazepam, sodium dichloroacetate, and hemodialysis were administered. The patient died at 45 months of age.
MRI, magnetic resonance imaging; CSF: cerebrospinal fluid.		

The prepared library was sequenced on the Illumina NextSeq platform (Illumina Inc., San Diego, CA, USA). The data were analyzed using SOPHiA DDM software (SOPHiA Genetics, Boston, USA) in conjunction with clinical findings. Informed consent for diagnostic and research studies was obtained from the patients' parents in accordance with the Declaration of Helsinki protocols.

DISCUSSION

Dysfunction of *FBXL4* leads to defects in mitochondrial fusion, mitophagy, and mitochondrial DNA maintenance, resulting in encephalomyopathic-type mitochondrial DNA depletion syndrome 13. The disease was first described in 2013 in two distinct patient groups, and more than 110 cases have been reported so far.^{5–22} In addition to the typical clinical presentation, findings, including small for gestational age, short stature, and feeding difficulties, have been described in the literature.⁴

Although microcephaly is present in approximately half of the patients reported in the literature, our patient has relative macrocephaly. Antenatal hydrocephalus was reported in only 1 patient, whereas dilated ventricles are more frequently reported in the literature.^{4,12,18,19,20} No patients have been reported in the literature with an indication for VP shunt due to severe hydrocephalus. Postoperatively, the patient experienced seizures and dystonia. It is unclear whether this was operation-related or related to the disease course.

Although the age of disease onset has been reported to range from the intrauterine period to 3 months of age, our patient's delayed presentation may be attributable to compensated lactic acidosis. Additionally, the impact of socioeconomic factors on delayed admission cannot be overlooked. However, it is possible that he did not experience an episode of lactic acidosis or hyperammonemia prior to his first admission, or that any episode was not severe enough to be noticed.

To date, survival in this disease is variable: the median age at death is two years (range: 2 days–75 months), although individuals surviving to 36 years of age have been reported.²³ It has also been reported that survival time is longer in individuals with missense variants than in those with null variants.⁴

To date, 6 splice-site mutations have been reported.^{4,24,25,26} In a case with a homozygous splice-site pathogenic variant, symptoms appeared on the first day of life; hyperammonemia, hearing loss, and cardiac findings were observed, findings that are reported in less than 50% of patients in reviews, and the patient died at 23 months of age.²⁶ In another case in which a compound-heterozygous splice-site pathogenic variant was reported, the age of onset was in the neonatal period, as in the previous case, and the patient was 4 years old and alive at the time of

publication.²⁵ Detailed clinical information about patients with other splice-site variants could not be obtained.^{4,24} Therefore, the relationship between splice-site variants and phenotypes could not be evaluated. However, upon examining patients with the described clinical findings, we do not have sufficient data to conclude that variants in the joint region are associated with early-onset disease. The c.1390-2A>G homozygous variant in the *FBXL4* gene identified in our patient represents a novel splice-site alteration between exons 7 and 8 that has not been reported previously. The more severe clinical findings observed in patients with splice-site variants may be due to these variants exerting a more deleterious effect on proteins through exon skipping, intron retention, and activation of cryptic splice sites. The c.1390-2A>G variant detected in this case can directly disrupt a critical splice site in the gene, leading to complete inhibition of protein synthesis or defective protein synthesis. This changes the acceptor splice site from the consensus sequence, thereby interfering with splicing.

Cranial MR imaging of the patient showed cerebral atrophy, involvement of the basal ganglia and white matter, a thin corpus callosum, and hydrocephalus, findings that are consistent with the literature. The finding that distinguishes the patient from the literature is that he had hydrocephalus severe enough to require shunt insertion. In addition, although less commonly reported in the literature, our patient had brainstem involvement, and no lactate peak was detected on MR spectroscopy despite high lactate levels.^{4,24}

During follow-up, the patient's encephalopathic periods were not always accompanied by lactic acidosis. This suggests that central nervous system manifestations of the disease are risk factors independent of its prognosis. Moreover, clinical deterioration associated with elevated lactic acid levels worsened during catabolic processes such as dehydration, infection, and surgery, making the patient's externalization difficult.

Furthermore, the history of SGA birth and dysmorphic features, observed in most patients described in the literature, may indicate that the *FBXL4* gene is also active during the intrauterine period.^{17,18,24}

Study Limitations

A key limitation of this report is that genetic testing was limited to a targeted panel of 4,493 genes rather than whole-exome or whole-genome sequencing. An additional genetic diagnosis contributing to the unusually severe hydrocephalus phenotype cannot be ruled out; a dual diagnosis remains possible. This limitation is explicitly acknowledged because further genomic studies are unavailable.

CONCLUSION

We aimed to contribute to phenotyping by reporting a patient with a novel variant in the *FBXL4* gene and a previously unreported clinical finding. Further studies and additional case reports are needed to clarify the function of *FBXL4* and to improve phenotyping.

Ethics

Informed Consent: Informed consent for diagnostic and research studies was obtained from the patients' parents in accordance with the Declaration of Helsinki protocols.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.T., M.S.K., Concept: A.N.A., Design: A.N.A., Data Collection or Processing: A.N.A., H.P., M.S.K., Analysis or Interpretation: A.N.A., H.P., Literature Search: A.N.A., Writing: A.N.A.

Conflict of Interest: The author(s) have no conflicts of interest to declare.

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