Case Report

# *NEXMIF* pathogenic variant in a female child with epilepsy and multiple organ failure: a case report

**Li Wang[#], Yongjian Huang[#], Xinglou Liu**

Department of Pediatrics, Tongji Hospital, Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

*Contributions:* (I) Conception and design: L Wang, X Liu; (II) Administrative support: Y Huang; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

*Correspondence to:* Xinglou Liu, MD, PhD. Department of Pediatrics, Tongji Hospital, Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Guanggu Campus, No. 501 Gaoxin Avenue, Hongshan District, Wuhan 430030, China. Email: liuxinglou@163.com.

**Background:** The neurite extension and migration factor (NEXMIF) gene encodes the neurite growth-directed factor whose main function is to play a role in neurite extension and migration for nerve development. It is associated with X-linked intellectual disability 98 and X-linked dominant inheritance, and its clinical manifestations mainly include intellectual disability, autistic behavior, poor development, dysmorphic features, gastroesophageal reflux, renal infection, and early seizures. Few cases of patients with NEXMIF variants had been reported, and to date, no deaths have been reported to our knowledge.

**Case Description:** We present a clinical report of a female child who had a history of epilepsy, and was diagnosed with multiple organ failure (MOF), sepsis, hemophagocytic lymphohistiocytosis, severe pneumonia, and pulmonary hemorrhaging. Genetic testing identified the NEXMIF variant c.937C>T (p.R313*) in this patient. Despite aggressive treatment with anti-inflammation drugs with methylprednisolone, plasma exchange, hemodialysis and mechanical ventilation, the patient died.

**Conclusions:** We reported the first case of the NEXMIF variant in a patient with the symptom of MOF, including acute liver failure and acute kidney injury (Grade 3). In addition, some complications, such as sepsis, hemophagocytic syndrome, pneumonia, and pulmonary hemorrhage, can also occur with this disease. All of these complications may have contributed to the patient's death. This report not only broadens the phenotype for NEXMIF variants but may also help physicians involved in the care of patients with this syndrome and enhance their understanding of this variant.

**Keywords:** Neurite extension and migration factor variant (*NEXMIF* variant); X-linked dominant inheritance; epilepsy; multiple organ failure (MOF); case report

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## Introduction

The neurite extension and migration factor (*NEXMIF*) gene, formerly named as KIAA2022 (Online Mendelian Inheritance in Man for gene: 300524), is located on the X chromosome (1) and is a gene which codes the X-linked mental retardation protein (2). The *NEXMIF* gene is highly expressed in fetal and adult brains, predominantly in the cerebral cortex and the cerebellum (3). It is also expressed to a lesser extent in other tissues (1).

NEXMIF pathogenic variants are associated with X-linked intellectual disability 98, autism spectrum disorder, and epilepsy (4-8). Previous reports on patients with *NEXMIF* gene pathogenic variants have noted that most males are severely affected, while most females have a milder phenotype or are asymptomatic (9-11). However,

a few affected female patients have been described (9-11). To date, no deaths related to the *NEXMIF* gene variant have been reported in either males or females. In this study, we report a case in which a female child patient with the *NEXMIF* variant with epilepsy, multiple organ failure (MOF), sepsis, hemophagocytic lymphohistiocytosis, severe pneumonia, and pulmonary hemorrhage died. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-435/rc).

## Case presentation

A 3-year-old female patient presented at pediatric department of Tongji Hospital, Affiliated to Tongji Medical College, Huazhong University of Science and Technology, with a complaint of an intermittent fever for 6 days, and drowsiness for 1 day. According to her parents, she was the second child born, and there was no family history of neurological disorders. The patient was a full-term, cesarean section baby, who was born to a non-consanguineous marriage, without any birth complications. She had suffered from a nodding spasm from the age of 1 year, for which she had received no treatment. She had no intellectual developmental disorder or developmental language delay. She also had no history of liver disease or substance abuse. Before being admitted to our hospital, she had been admitted to another hospital because of intermittent seizures half a month ago. In that hospital she had done the following examinations. The electroencephalogram (EEG) results showed spiked, slow waves, multi-spiked slow waves, generalized spiked waves, and a decreasing dominant rhythm in the occipital region (*Figure 1*). The video-EEG results showed some myoclonic seizures (*Figure 2*). No positive findings were found in the routine blood, liver function, kidney function, or electrolyte test results, or the computed tomography scan of the head. The patient was diagnosed with epilepsy and myoclonia and started taking sodium valproate (160 mg per dose, twice a day, orally). The patient's epilepsy was then well controlled, and she was discharged and instructed to continue the oral sodium valproate treatment.

After admission to our hospital, we performed routine blood tests, and liver function, kidney function, electrolyte, and other routine examinations. Unsurprisingly, the examinations suggested MOF and hemophagocytic syndrome, and the patient was soon transferred to the Pediatric Intensive Care Unit. Upon physical examination at admission, she had jaundice, and drowsiness, and she had been in a state of anuria since admission. She also had a bilateral pupil size, sensitivity to light reflex, a temperature of 36.8 ℃, a pulse rate of 103 beats per minute, a respiratory rate of 22 breaths per minute, a blood pressure of 109/67 mmHg, and 99% oxygen saturation. Her height and body weight were 103 cm [+1 standard deviation (SD)] and 17 kg (+1 SD), respectively. The physical examination of the patient revealed pharyngeal congestion, low and dull cardiac sounds, and hepatomegaly. No other abnormalities were noted.

The patient's laboratory findings are summarized in *Table 1*. Her minimum hemoglobin and platelet levels were 77 g/L and $68\times10^9$/L, respectively. Her troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were markedly elevated. The laboratory findings also revealed hyperbilirubinemia and hypoalbuminemia. The patient had no dyslipidemia, including hypertriglyceridemia. Her serum creatinine level was significantly elevated, and an electrolyte disturbance was detected. Her prothrombin time (PT), activated partial thromboplastin time (APTT) and D-dimer were notably increased, and her fibrinogen was decreased. The patient's interleukin-2 receptor level, serum ferritin, serum aminotransferases, and lactate dehydrogenase were above the upper limits of normal. The tests also showed hyperlactatemia and hyperammonemia. Pathogen testing, including metagenomic pathogen-next-generation sequencing, respiratory pathogen antibody

**Highlight box**

**Key findings**

- The female child had a heterozygous chrX:73963455, NM_001008537, c.937C>T (p.R313*) variant in the *NEXMIF* gene.

**What is known and what is new?**

- We reported a case of a patient with the *NEXMIF* variant and showing the symptom of multiple organ failure (MOF).
- The *NEXMIF* variant may occur in patients with the symptom of MOF; however, sodium valproate can also cause MOF. Caution should be exercised when treating patients with the *NEXMIF* variant with sodium valproate.

**What is the implication, and what should change now?**

- Variants in the X-chromosomal *NEXMIF* gene can lead to symptoms with epilepsy, myoclonia, and MOF. This case report reminds doctors to rule out genetic metabolic disorders before administering sodium valproate, and to regularly perform routine blood, liver function, kidney function, and electrolyte level tests when treating patients with sodium valproate.

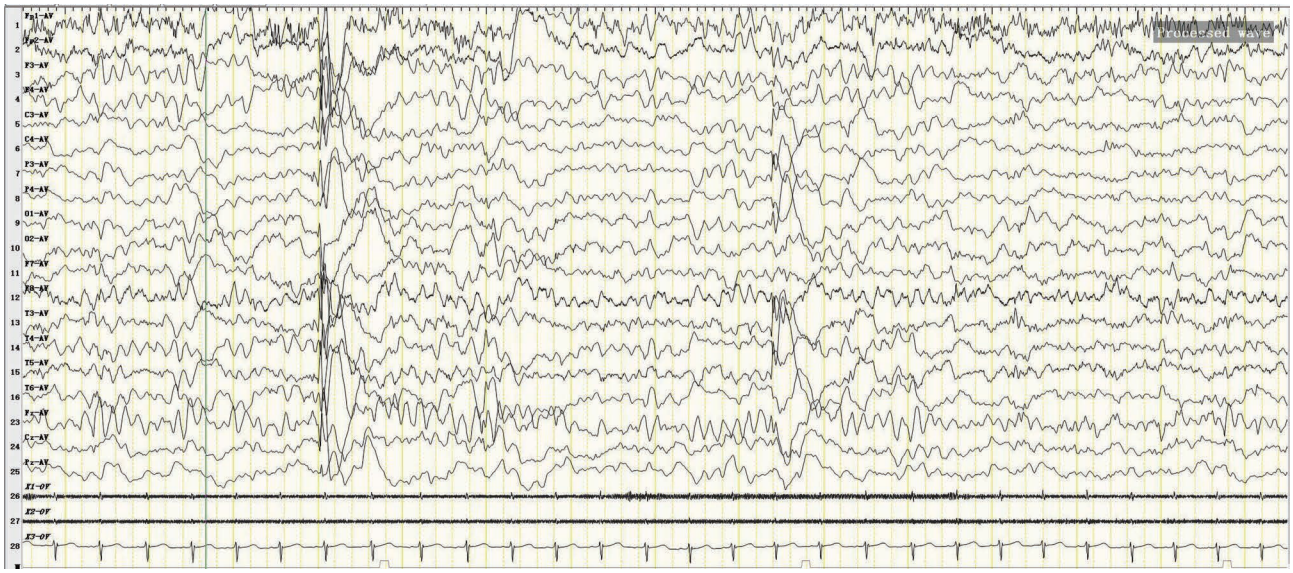


**Figure 1** The electroencephalogram of the awake patient showed spiked slow waves, multi-spiked slow waves, generalized spiked waves, and a dominant rhythm decrease in the occipital region.

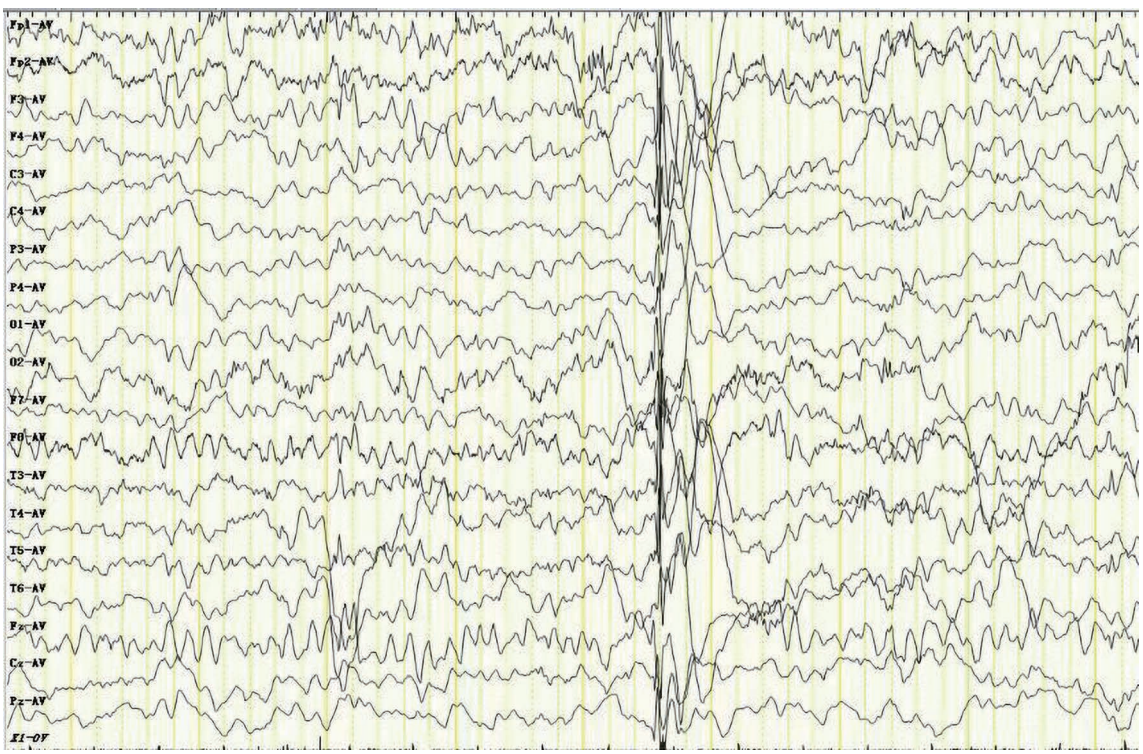


**Figure 2** Myoclonic seizures were detected in the awake patient.

**Table 1** Laboratory findings

| Days after admission | Normal range | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| WBC ($\times10^9$/L) | 4–12 | 3.55 | 12.8 | 8.08 | 8.74 | 13.21 | 17.06 | 19.92 |
| HB (g/L) | 110–145 | 131 | 120 | 77 | 81 | 107 | 107 | 97 |
| PLT ($\times10^9$/L) | 150–450 | 124 | 147 | 68 | 98 | 145 | 163 | 147 |
| cTnI (pg/mL) | <15.6 | 11.1 | – | 116.2 | 45.5 | 74.9 | 138.3 | 211.4 |
| Lactose (mmol/L) | 0.5–2.2 | 4.57 | 14.53 | 6.42 | 8.89 | 6.54 | 6.99 | 6.09 |
| NT-proBNP (pg/mL) | <300 | – | 2,066 | 3,433 | 8,401 | 7,162 | 5,801 | 2,872 |
| Ferritin (μg/L) | 30–400 | >50,000 | 25,937 | 19,010 | 5,865.6 | 3,888.2 | 1,899.2 | 1,305 |
| ALT (U/L) | <41 | >7,000 | 2,689 | 1,958 | 690 | 539 | 262 | 131 |
| AST (U/L) | <40 | >7,000 | 4,567 | 2,523 | 585 | 275 | 205 | 131 |
| Total serum bilirubin (μmol/L) | <26 | 78.3 | 101.5 | 103.1 | 135.6 | 193.7 | 186.9 | 164.5 |
| Triglycerides (mmol/L) | <1.7 | 1.49 | 0.12 | 0.12 | 0.54 | 1.67 | 1.57 | 1.5 |
| Total cholesterol (mmol/L) | <5.81 | 1.43 | <0.1 | 1.27 | 1.95 | 1.13 | 2.2 | 2.69 |
| Creatine kinase (U/L) | <170 | 254 | 139 | 461 | 890 | 758 | 963 | 1,644 |
| LDH (U/L) | 120–300 | >1,867 | >1,867 | >1,867 | 747 | 679 | 698 | 952 |
| γ-GT (U/L) | 6–42 | 132 | 89 | 75 | 54 | 50 | 47 | 52 |
| Alpha fetoprotein (ng/mL) | <7 | – | – | – | 3.48 | – | 74.75 | – |
| Urea (mmol/L) | 1.7–8.3 | 22.10 | 10.2 | 10.4 | 7 | 6.2 | 8 | 10 |
| Creatinine (μmol/L) | 45–84 | 291 | 267 | 350 | 289 | 281 | 314 | 297 |
| CRP (mg/L) | <3 | 13 | 5.2 | 4.7 | 3 | 3 | 3.3 | 4.3 |
| Blood ammonia (μmol/L) | 11–51 | 335 | 457 | 250 | 269 | 261 | 185 | 214 |
| PT (s) | 12–14.5 | 43.5 | 56.4 | 50.5 | 29.3 | 38 | 24.3 | 19.9 |
| APTT (s) | 34–47 | 51.3 | 59.6 | 63.9 | 44.4 | 65.6 | 69.2 | 103 |
| Prothrombin activity (%) | 75–125 | 17% | 13% | 14% | 28% | 20% | 36% | 48% |
| INR | 0.8–1.2 | 4.63 | 6.42 | 5.58 | 2.81 | 3.90 | 2.18 | 1.69 |
| Fibrin degradation product (μg/mL) | <5 | 20.1 | 35.9 | 41.1 | 84.1 | 97 | 113.5 | 104.7 |
| D-dimer (μg/mL FEU) | <0.5 | 6.26 | 8.43 | 6.55 | 22.57 | 21.57 | 37.01 | 28.93 |
| Fibrinogen (g/L) | 1.8–4 | 0.94 | 1.08 | 1.94 | 1.55 | 0.6 | 1.34 | 1.44 |
| TNF-α (pg/mL) | <8.1 | 57 | 30.4 | – | 19.7 | – | 21.6 | 25.6 |
| Interleukin 6 (pg/mL) | <7 | 217.9 | 96.79 | – | 50.77 | – | 160.3 | 130.4 |
| Interleukin-2 receptor (U/mL) | 223–710 | >7,500 | 3,806 | – | 3,002 | – | 3,430 | 2,715 |

WBC, white blood cell; HB, hemoglobin; PLT, platelet; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; γ-GT, γ-glutamyl transpeptidase; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; TNF-α, tumor necrosis factor-α.

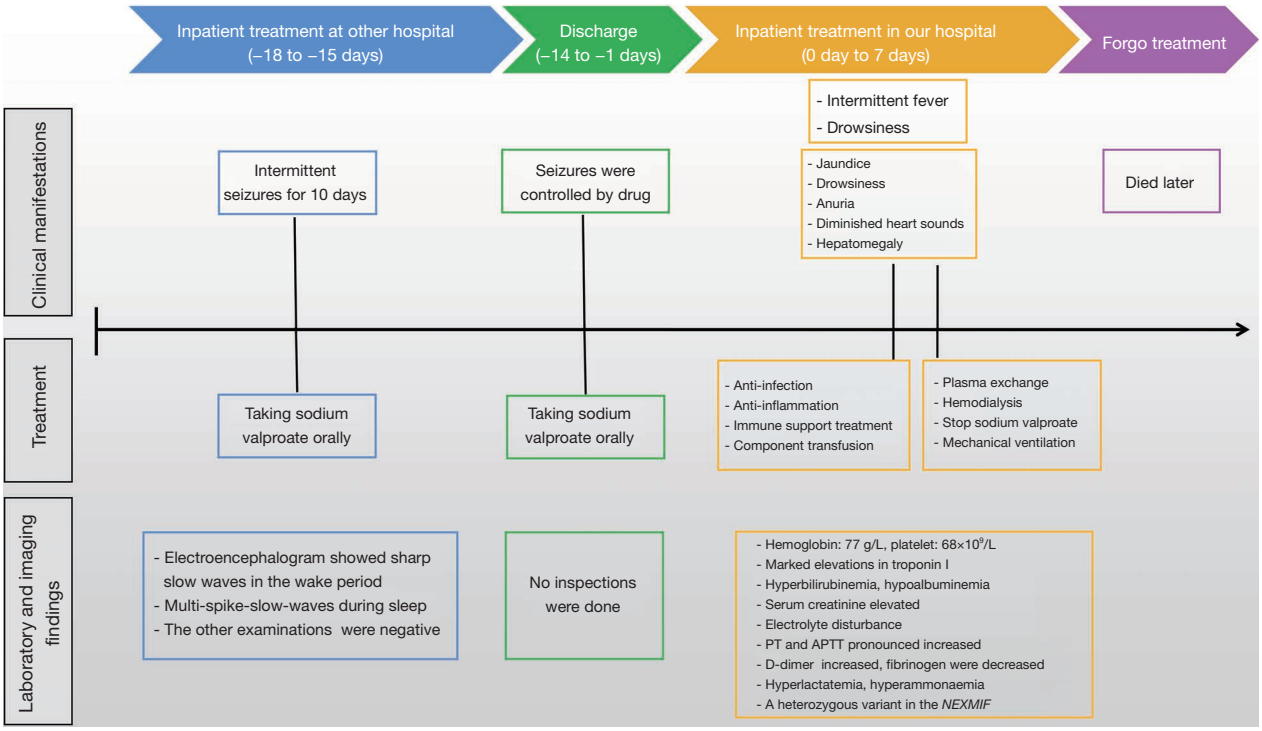


**Figure 3** Historical and current information for the patient.

testing, blood cultures, and sputum cultures, was performed before treatment. However, there were no positive findings.

An abdominal ultrasound showed hepatomegaly and a thickening of the gallbladder wall. No positive findings were found on the cardiac ultrasound or the kidney ultrasound. These results suggested MOF, including acute liver failure (e.g., abrupt onset signs of drowsiness, hyperammonemia, serum aminotransferases, a lactate dehydrogenase level above the upper limit of normal, the progressive aggravation of jaundice, hemorrhagic tendency with an international normalized ratio ≥1.5, and prothrombin activity ≤40%), grade 3 acute kidney injury (e.g., anuria, and a glomerular filtration rate <35 mL/min/1.73 $m^{-2}$), and disseminated intravascular coagulation (e.g., a platelet count <100×$10^9$/L, fibrinogen 1.5 g/L, serum fibrin degradation products >20 mg/L). The PT, APTT, and d-dimer were notably increased. The patient also had hemophagocytic syndrome (e.g., a fever, hepatomegaly, drowsiness, anemia, hyperbilirubinemia, hypoalbuminemia, elevated liver enzymes, hypofibrinogenemia, prolonged APTT and PT, elevated serum cytokines, including interleukin-2 receptor, interleukin-6, necrosis factor-α, and elevated ferritin). Thus, anti-infection drugs with meropenem, anti-inflammation drugs with methylprednisolone, plasma exchange, hemodialysis, immunosupportive therapy, component transfusion, and organ protection were promptly initiated. Sodium valproate was discontinued, as it has been linked to multiple organ-dysfunction syndromes (12).

About 36 hours after admission, the patient developed a pulmonary hemorrhage and respiratory failure. Mechanical ventilation assisted her respiratory failure. As the patient had epilepsy and MOF, we also considered a diagnosis of a genetic metabolic disease, such as Alpers-Huttenlocher syndrome.

After informed consent was obtained, genomic DNA was extracted from peripheral blood samples of the patient, and her parents for molecular genetic analysis. Plasma exchange and hemodialysis was performed 4 times and 5 times separately during the procedure. Unfortunately, the patient's condition did not improve. She remained unconscious and had anuria. Regrettably, the MOF could not be corrected, and her parents decided to forgo treatment. The patient died later (*Figure 3* outlines the patient's history).

Whole exome sequencing, which was performed 1 month later, revealed that the patient had a heterozygous variant of chrX:73963455, NM_001008537, c.937C>T (p.R313*) in the *NEXMIF* gene, and other variants (see Table S1). However, the mitochondrial genetic tests showed no

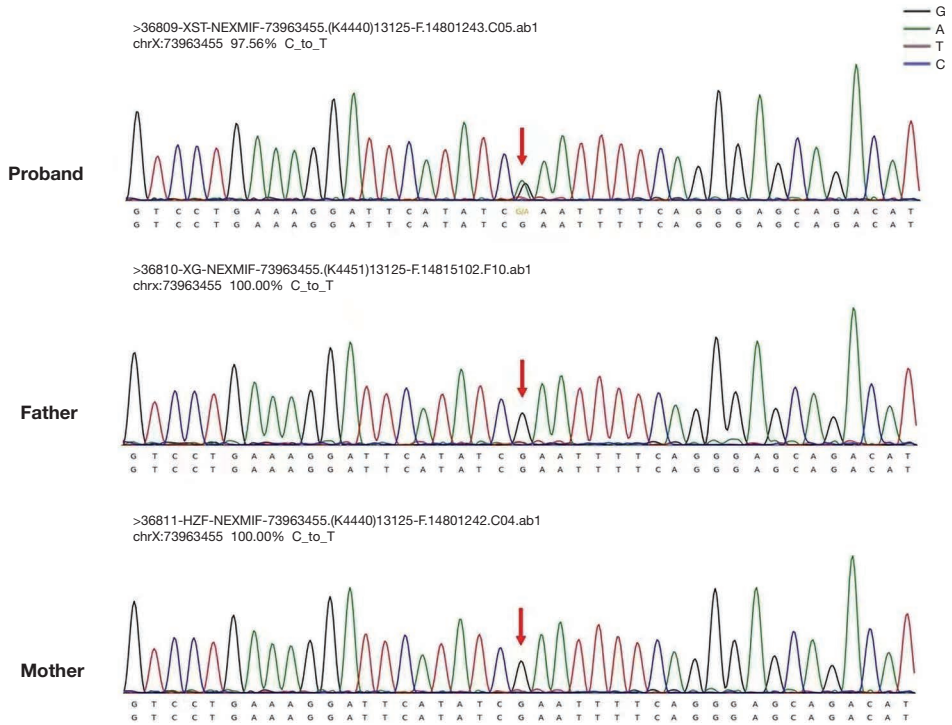


**Figure 4** The heterozygous variant in the NEXMIF gene of the proband and her parents.

abnormalities. A Sanger-sequencing analysis of the parents did not detect any pathogenic variants, which suggests that the change arose *de novo* in this patient (*Figure 4*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and with the Helsinki Declarations (as revised in 2013). Written informed consent was obtained from the patient's parents or legal guardians for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Discussion

The *NEXMIF* gene is expressed in multiple tissues during development but is highly expressed in the fetal and adult brain and plays an important role in neuronal development (1). A pathogenic variant of the gene can cause aberrant neuronal migration and major defects in the apical dendrite growth and orientation, leading to a premature stop codon or larger structural variants (13). Thus, the underlying mechanism is likely a loss of function, ranging from a total loss of function with no protein expression in hemizygous males to a partial loss of function with a variable decrease in the protein expression in females. Abnormalities in synaptogenesis and synaptic function are key underlying factors that lead to social and cognitive deficits during brain development (14).

Clinically, the *NEXMIF* variant has been reported to present in patients with intellectual disabilities (7), refractory seizures (7), impaired language development (7), autism (15), dysmorphism (8), microcephaly (8), postnatal growth retardation (5), obesity (16), hypotonia (16), and spasticity (16). It can occur in both males and females. It was first reported in 2 related males with severe to profound intellectual disabilities, autism, absent language development, and dysmorphic facial features (1). According to a review (6), females usually have a less severe phenotype than males, and the occurrence of facial dysmorphism, microcephaly, hypotonia, growth retardation, and feeding difficulties is less frequent in females than males, but surprisingly, epilepsy is more commonly reported in females. In female patients, 74% of patients have mixed or generalized epilepsy, and the most common seizures are myoclonic (13).

There is no specific medicine for the *NEXMIF* variant, and it can only be treated according to the symptoms. In the present case, the patient also had seizures, but she did not have any of the other symptoms that had been reported

in the literature, such as intellectual disabilities, impaired language development, autism, dysmorphism, microcephaly, postnatal growth retardation, and obesity. However, the patient had other severe symptoms, including MOF, disseminated intravascular coagulation, and hemophagocytic syndrome. Thus, the variant may cause serious symptoms.

Sodium valproate is an important drug in the treatment of epilepsy, with the broadest spectrum used in all types of seizures and syndromes. The side effects of sodium valproate include diarrhea, spasm of the gastrointestinal tract, constipation, tremors, ataxia, pancreatitis (17), thrombocytopenia, liver function impairment, and MOF (17). In general, sedation, tremors, headache, ataxia, dizziness, and gastrointestinal complaints, such as nausea, vomiting, and indigestion, are observed at the onset of therapy and are either transient or respond to decreasing the dose of sodium valproate (18). Hepatic toxicity of sodium valproate is usually seen within the first 2 months of therapy but can occur after years of therapy (19). Within the first 3 months of therapy, up to 44% of patients treated with sodium valproate have increased liver enzymes (12).

The withdrawal of sodium valproate or decreasing the dose results in laboratory tests returning to normal and the alleviation of any symptoms, which may lead to a better prognosis. However, a few patients progress rapidly, and fatal hepatitis is often associated with sodium valproate. Fatal hepatitis is idiosyncratic and not related to the serum level of sodium valproate. Patients with idiosyncratic sodium valproate-related hepatitis present with impaired consciousness, anorexia, nausea, vomiting, or loss of seizure control (17). In such circumstances, the drug should be stopped as soon as possible. However, even after the discontinuation of the medication, patients may progress to fulminant hepatic failure and death. After sodium valproate is started, patients' hematological parameters need to be checked regularly to detect any adverse drug reactions as early as possible.

According to the literature, sodium valproate has been used in some patients with the *NEXMIF* variant to control epileptic symptoms. Panda (20), Morave (21), and Wu (22) reported no adverse drug reactions related to sodium valproate in the patients in their studies. However, Ogasawara (16) reported amenorrhea after sodium valproate use in patients.

In our study, the patient had a history of taking sodium valproate. About 2 weeks after the patient began taking sodium valproate, her laboratory results showed a marked increase in serum transaminases, and elevations in serum ammonia and bilirubin, and a prolongation of the PT. It may be that the patient suffered from sodium valproate-related hepatitis. The patient had no history of liver disease, and no history of substance abuse, and her hepatitis serologies were negative. Her ultrasound results showed no structural cause for her hepatic failure.

Sodium valproate can also cause pancreatitis, which usually occurs alone but occasionally accompanies hepatic failure. The patient also suffered from pancreatitis. Another unique aspect of this case, is that the patient also suffered from acute kidney injury (Grade 3), disseminated intravascular coagulation, acidosis, electrolyte disturbances, and drowsiness.

Alpers-Huttenlocher syndrome is an autosomal recessive disease. It is an enzyme abnormality caused by a genetic variant. The resulting decrease in mitochondrial DNA causes mitochondrial DNA depletion syndrome and reduced polymerase-gamma enzyme activity (25). The syndrome is divided into the early onset type and late-onset type. The hallmark triad clinical features of Alpers-Huttenlocher syndrome include intractable seizures, developmental regression, and liver dysfunction. The age at onset is influenced, in part, by specific variants within the polymerase-g gene, other genes (24), and environmental factors, such as viral infections, and certain medications, such as sodium valproate. In the present case, the patient had an induction factor of taking sodium valproate, with a presentation of seizure and liver dysfunction, but without developmental regression. Thus, we did not consider whether or not the patient had Alpers-Huttenlocher syndrome.

We conducted whole exome sequencing and mitochondrial DNA sequencing for the patient, but no variants were found in her mitochondrial DNA. Genetic testing identified the *NEXMIF* variant c.937C>T (p.R313*) in this patient. To date, no severe cases of *NEXMIF* variants have been reported in patients with MOF. Thus, the findings in this article about the patient's MOF may extend the features of the *NEXMIF* variant.

Encephalopathy caused by variants in the *NEXMIF* gene may cause serious complications in females. Multiple organ-dysfunction syndrome may also be caused by sodium valproate. Thus, we cannot determine whether the MOF was caused by *NEXMIF* variant or sodium valproate. This is an inadequacy of this report and should serve to remind us that in treating children with epilepsy, consideration needs to be given to some genetic metabolic diseases, gene variants, and other diseases before sodium valproate

**Table 2** Clinical data of previously described patients with the NEXMIF variant

| Literature | Sex, age (years) | Consanguinity | Clinical symptoms | Genetic testing |
|---|---|---|---|---|
| Lorenzo *et al.* (25) | M, 11 | No | Grand mal seizures, and autistic behavior | KIAA2022: c.652C>T(p.R218*) |
| Lorenzo *et al.* (25) | M, 10 | No | Generalized tonic-clonic seizures, vomiting, and constipation | KIAA2022: c.2707G>T(p.E903*) |
| Webster *et al.* (7) | F, 8 | No | Developmental delay, limited language, hyperactive, inattentive, and epilepsy | De novo 14-nucleotide deletion (c.3053_3066del14, p.G1018Dfs*2) in KIAA2022 |
| Webster *et al.* (7) | F, 11 | No | Generalized tonic-clonic seizures, developmental delay, and limited language | De novo nonsense c.652 C>T, p.R218* mutation in KIAA2022 |
| Webster *et al.* (7) | F, 11 | No | Developmental delay, babbling, hyperactive, myoclonic seizures, and atonic drop seizures | De novo frameshift mutation, c.422delA, p.Q141Rfs*7 in KIAA2022 |
| Webster *et al.* (7) | F, 6 | No | Developmental delay, attention difficulties, myoclonic seizures, and epilepsy | De novo duplication, c.625dupC, p.L209Pfs*3 mutation in KIAA2022 |
| Webster *et al.* (7) | F, 7 | No | Generalized epilepsy, and developmental delay | De novo nonsense c.937C>T (p.R313*) mutation in KIAA2022 |
| Samanta *et al.* (25) | F, 9 | No | Seizures, developmental delay, and attention deficit hyperactivity disorder | De novo frameshift mutation of KIAA2022 with 4 nucleotides missing at position 1718_1721 |
| Lambert *et al.* (15) | F, 29 | N/A | Attention deficit, learning disabilities, language impairment, and generalized epilepsy | NEXMIF exon 3: NM_001008537.2:c.3470C>A:p.(S1157*) |
| Ogasawara *et al.* (16) | F, 46 | No | Speech delay, intellectual disability, and generalized tonic-clonic seizures | Heterozygous de novo mutation, c.1123del (p.E375Rfs*21) in NEXMIF |

is administered. After sodium valproate is administered, blood tests should be conducted regularly to avoid adverse reactions as early as possible.

To investigate the variants of *NEXMIF*, we searched for articles that had been published in the last 5 years using the keyword of "*NEXMIF*." The following *NEXMIF* variants (see summary in *Table 2*) have been reported: c.652C>T (p.R218*) (25), *NEXMIF*: c.2707G>T (p.E903*) (25), *de novo* 14-nucleotide deletion (c.3053_3066del14, p.G1018Dfs*2) in *NEXMIF* (7), *de novo* nonsense c.652C>T (p.R218*) variant in *NEXMIF* (7), *de novo* frameshift variant, c.422delA, p.Q141Rfs*7 in *NEXMIF* (7), *de novo* duplication, c.625dupC, p.L209Pfs*3 variant in *NEXMIF* (7), *de novo* nonsense c.937C>T (p.R313*) variant in *NEXMIF* (7), *de novo* frameshift variant of *NEXMIF* with 4 nucleotides missing at position 1718_1721 (25), *NEXMIF* exon 3: NM_001008537.2: c.3470C>A: p (S1157*) (15), and heterozygous *de novo* variant, c.1123del (p.E375Rfs*21) in *NEXMIF* (16).

Genetic testing identified the *NEXMIF* variant of c.937C>T (p.R313*) in the patient in this study, and simultaneous sequencing data showed that the patient's parents did not carry the variant, which may have occurred *de novo*. This rare variant was previously reported in 2016 (7) in a woman who carried the new variant. The medical conditions of that woman included intellectual disabilities, medically refractory seizures, anxiety, tantrums, impaired language development, gastroesophageal reflux in infancy, constipation, encopresis, and a kidney infection that required hospitalization. To date and to our knowledge, this variant has not been reported in any reference population genetic database. The nonsense c.937C>T (p.R313*) variant in *NEXMIF* produces a truncated 312 amino acid product. This article may extend the gene variant library and thus provide a basis for the study of the *NEXMIF* variant.

## Conclusions

In conclusion, we showed that variants in the X-chromosomal *NEXMIF* gene can lead to symptom in

females with epilepsy, myoclonia, MOF, including acute liver failure, acute kidney injury (Grade 3), disseminated intravascular coagulation, and hemophagocytic syndrome. Unfortunately, we could not confirm whether the patient's MOF was caused by the genetic variant or sodium valproate. However, this case report should remind doctors to rule out genetic metabolic disorders before administering sodium valproate, and to regularly conduct routine blood, liver function, kidney function, and electrolyte level tests.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-435/rc

*Peer Review File:* Available at https://tp.amegroups.com/article/view/10.21037/tp-22-435/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-435/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents or legal guardians for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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## Supplementary

**Table S1** List of VUS, PP or P variants

| Gene symbol | OMIM code | Inheritance | HG 19 location | Transcript | Nucleotide and amino acid | Zygotic state | Population frequency | ACMG variation classification | Related diseases | Variation source |
|---|---|---|---|---|---|---|---|---|---|---|
| *ADA2* | 607575 | AR | chr22:17669245 | NM_017424 | c.1065C>A(p.F355L) | Heterozygote | 0.003; East Asia | VUS | Autoimmune vasculitis-immunodeficiency-Blood deficiency syndrome/?Sneddon syndrome | Father |
| *ADAR* | 146920 | AR/AD | chr1:154560739 | NM_001111 | c.2886-5T>C | Heterozygote | <0.001 | VUS | Aicardi Goutieres syndrome/ Dyschromatosis symmetrica hereditaria | Father |
| *B4GALT1* | 137060 | AR | chr9:33120603 | NM_001497 | c.650C>T(p.A217V) | Heterozygote | 0.001; East Asia | VUS | Congenital disorder of glycosylation type IId | Mother |
| *DUOX2* | 606759 | AR | chr15:45396563 | NM_014080 | c.2335G>A(p.V779M) | Heterozygote | 0.004; East Asia | VUS | Thyroid hormone production disorder type 6 | Mother |
| *FBN1* | 134797 | AD | chr15:48717589 | NM_000138 | c.7430A>G(p.Q2477R) | Heterozygote | <0.001 | VUS | Acromegaly dysplasia/Marfan syndrome | Father |
| *G6PD* | 305900 | XL | chrX:153762317 | NM_000402 | c.793C>T(p.L265F) | Heterozygote | <0.001 | VUS | Glucose-6-phosphate Dehydrogenase | Mother |
| *GYS2* | 138571 | AR | chr12:21699327 | NM_021957 | c.1500T>A(p.C500*) | Heterozygote | – | PP | Hepatic glycogen storage type 0a | Mother |
| *SLC37A4* | 602671 | AR | chr11:118897728 | NM_001164278 | c.703G>T(p.V235L) | Heterozygote | 0.001; East Asia | VUS | Glycogen storage disease type 1b/ Glycogen storage disease type 1c | Mother |
| *SPATA5* | 613940 | AR | chr4:123857310 | NM_145207 | c.1333C>T(p.R445*) | Heterozygote | <0.001 | PP | Epilepsy-hearing impairment-mental retardation syndrome | Father |
| *SRD5A2* | 607306 | AR | chr2:31754395 | NM_000348 | c.680G>A(p.R227Q) | Heterozygote | 0.006; East Asia | P variants | 5α-reductase deficiency type 2 | Mother |
| *STEAP3* | 609671 | AD | chr2:31754395 | NM_182915 | c.1492G>A(p.V498I) | Heterozygote | <0.001 | VUS | Hypochromic anemia with iron overload type 2 | Father |

AR, autosomal recessive; AD, autosomal dominant; XL, X-linked; VUS, variant uncertain significance; PP, possibly pathogenic; P variants, pathogenic variants.


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