Torpedo Maculopathy Associated with *NEXMIF* Mutation

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Established Facts

- *NEXMIF* is located in the X chromosome and encodes neurite extension and migration factor.
- Mutations in *NEXMIF* are a rare cause of X-linked intellectual disability, with only 15 affected males described in the literature.
- In addition to global developmental impairment, males with *NEXMIF* mutations may have autistic features, hypotonia, growth retardation, and subtle dysmorphic features.
- There have been 24 reported females with *NEXMIF* mutations; however, the phenotype more commonly involves milder intellectual disability with drug-resistant epilepsy.

Novel Insights

- Torpedo maculopathy, a rare ophthalmologic abnormality, is described in a boy with a novel de novo *NEXMIF* mutation.
- On review of previously published cases, ophthalmologic abnormalities were reported in 7 of the 15 previously published males with *NEXMIF* mutations.
- *NEXMIF* may play a role in eye development.
- An ophthalmologic evaluation should be undertaken in any patient with *NEXMIF* mutation.

Keywords

Generalized epilepsy · *NEXMIF* · Torpedo maculopathy · X-linked intellectual disability

Abstract

Mutations in the neurite extension and migration factor (*NEXMIF*) gene are associated with X-linked intellectual disability. Thus far, all males reported with *NEXMIF* mutations

have mild to profound intellectual disability with varying combinations of autistic features, poor or absent speech, epilepsy, facial dysmorphism, and strabismus. Affected females tend to have milder intellectual disability but severe, drug-resistant epilepsy. Here, we present a 32-month-old boy with a novel de novo frameshift *NEXMIF* pathogenic variant (p.Glu375ArgfsX21) who has mild motor delay, language delay, autistic features, and strabismus. In addition to these commonly described findings of *NEXMIF* mutations, his fun-

dus exam revealed a very rare ophthalmologic abnormality, torpedo maculopathy. This finding has not previously been reported with *NEXMIF* mutation; however, on literature review, 7/15 males with *NEXMIF* mutations had other ophthalmologic abnormalities. This patient expands the phenotypic spectrum for males with *NEXMIF* mutations and suggests that *NEXMIF* may play an important role in ocular development.

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Intellectual disability (ID) is an early-onset neurodevelopmental disorder characterized by impairment in intelligence and adaptive skills [American Psychiatric Association, 2013]. The estimated prevalence of ID is around 2–3% in Western countries with a male predominance (relative risk of 1.6–1.7) [Leonard and Wen, 2002]. This male gender bias has been partially explained through the identification of genes associated with ID in the X chromosome. At present, over 100 genes have been implicated in X-linked ID [Lubs et al., 2012].

NEXMIF (OMIM 300524), formerly known as *KIAA2022*, is an X chromosome gene associated with X-linked ID [Cantagrel et al., 2004] and encodes neurite extension and migration factor. To date, 15 males with pathogenic *NEXMIF* variants have been reported [Cantagrel et al., 2004; Van Maldergem et al., 2013; Charzewska et al., 2015; Kuroda et al., 2015; Lambert et al., 2018; Lorenzo et al., 2018]. All affected males have global developmental impairment ranging from profound to mild. They usually show a wide range of clinical manifestations that includes autistic features, hypotonia, postnatal growth retardation, and subtle dysmorphic features [Cantagrel et al., 2004; Van Maldergem et al., 2013; Charzewska et al., 2015; Kuroda et al., 2015; Lambert et al., 2018; Lorenzo et al., 2018]. Seizures have been reported in 9 of the 15 (60%) reported male patients thus far and are almost always generalized in nature (Table 1). Strabismus and keratoconus have been previously described in some patients; however, maculopathy has not been reported. There have also been 24 affected females reported with pathogenic *NEXMIF* variants; however, the phenotype more commonly involves drug-resistant epilepsy and milder ID [de Lange et al., 2016].

Here, we describe a 32-month-old boy with a novel frameshift *NEXMIF* pathogenic variant who has a very rare ophthalmologic pathology, torpedo maculopathy, in addition to developmental impairment and generalized spike-wave on EEG.

Fig. 1. Axial T2-weighted brain MRI of our patient at 28 months of age, showing increased extra-axial spaces around frontal regions (arrows).

Case Report

We reviewed the Epilepsy Pharmacogenomics Research Database at the Montreal Children's Hospital for patients with variants in *NEXMIF* and identified 1 patient.

The patient is the second child of unrelated healthy Syrian parents with no known family history of developmental delay or autism. Following an uncomplicated pregnancy, he was delivered at 39 weeks by cesarean section due to mild spotting and history of severe back pain with previous pregnancy. He weighed 3.2 kg at birth had a normal perinatal course other than mild feeding difficulty requiring nasogastric feeding for the first 2 days of life.

From a developmental perspective, he showed global delay from early infancy. Language was most severely affected with his first word coming at approximately 2.5 years. He did not sit until 9 months and walked at 19 months. At 32 months, he had just learned to feed himself with a spoon. His parents were also concerned about his behavior, reporting that he engaged in head banging. There was no history of regression.

At 9 months of age, his parents noticed some unusual staring spells, leading to an EEG which showed generalized spike-wave discharges. However, the staring spells were felt unlikely to be seizures as he was responsive throughout; they subsequently resolved without antiepileptic medication. He has not had any definite seizures.

On physical examination at 27 months, his head circumference was 50 cm (50th percentile) and weight 17 kg (95th percentile). He had mild facial dysmorphic features including bulbous nose and upslanting palpebral fissures. On skin examination, a large café-au-lait macule was noted on the right buttock. Motor exam revealed normal muscle bulk, slightly increased appendicular tone, and brisk reflexes. He was referred to ophthalmology because of the staring spells and was found to have strabismus, mild astigmatism, and torpedo maculopathy. His evaluation by a speech therapist confirmed severe receptive and expressive language difficulties as well as atypical interaction, interests, and behaviors.

A genetic disorder was suspected, and a panel of metabolic and genetic tests, as well as brain MRI, was arranged.

Results

The results of a panel of metabolic tests were normal, including plasma testing for amino acids, acylcarnitine profile, ammonia, creatine kinase and lactate as well as urine organic acids. MRI of the brain demonstrated increased extra-axial spaces in the frontal regions (Fig. 1). Comparative genomic hybridization microarray did not show any copy number variants, and Fragile X testing was normal. An autism/ID trio gene panel (GeneDx) identified a de novo pathogenic variant p.Glu375ArgfsX21 (c.1123delG) in *NEXMIF*.

Discussion and Conclusion

We report a boy with global developmental delay and autistic behavior due to a novel *NEXMIF* pathogenic variant, further clarifying the spectrum of abnormalities which may be associated with mutations in this gene. To our knowledge, this is the sixteenth male reported with a *NEXMIF* pathogenic variant. The patient shares many features in common with previously published reports, but there are some previously undescribed clinical aspects as well [Cantagrel et al., 2004; Van Maldergem et al., 2013; Lorenzo et al., 2018].

Our patient has torpedo maculopathy, a very rare form of maculopathy for which there has not previously been strong evidence to suggest an underlying genetic etiology. Torpedo maculopathy has an estimated prevalence of 2 in 100,000 and is characterized by hypopigmented oval-shaped (“torpedo-like”) lesions located temporal to the macula [Shirley et al., 2018]. These lesions are typically unilateral, usually nonprogressive, and do not affect central visual acuity [Shirley et al., 2018]. Therefore, torpedo maculopathy is usually diagnosed in asymptomatic individuals during routine eye examination by recognition of its typical structure and location. However, though torpedo maculopathy is considered by many to be a benign finding, there are cases of patients with associated choroidal neovascularization and consequent visual field defects, so patients should have ongoing ophthalmologic follow-up or at least counseling regarding the potential risks [Shirley et al., 2018]. Our patient has a *NEXMIF* pathogenic variant; the only previous association of torpedo maculopathy

Table 1. Male patients with ophthalmologic abnormalities and/or seizures

Patient	Cantagrel et al., 2004			Van Maldergem et al., 2013			Charzewska et al., 2015		Lorenzo et al., 2018			Lambert et al., 2018		Present case
	1	2	3	4	5	6	7	8	9	10	11			
Age	12 years	6 years	4 years	10 years	40 years	8 years	-	-	19 years	10 years	7 years	7 years	32 months	
Mutation	inv(X) (p22.3q13.2)	c.3597insA, p.Ser1200Tyrfs*5	c.3597insA, p.Ser1200Tyrfs*5	c.183delC, p.Arg62Glufs*5	c.183delC, p.Arg62Glufs*22	Xq13 duplication	Xq13 duplication	c.652C>T, p.Arg218*	c.2707G>T, p.Glu903*	c.3470C>A, p.Ser1157*	c.1123delG, p.Glu375Argfs*21			
Ophthalmologic pathology	Strabismus	Strabismus	Strabismus	-	-	Right squint	-	Strabismus and keratoconus	Strabismus and cerebral visual impairment	Strabismus	Strabismus and torpedo maculopathy			
Age of seizure onset	13 months	1 month	Unclear	7 years	14 years	-	-	-	-	6 months	-			
Seizure type(s)	GTC	Epileptic spasms	Epileptic spasms	Absence, atonic	“Generalized epilepsy”	-	-	Generalized	Febrile GTC	Epileptic spasms, FIAS, myoclonic	-			
EEG	Bilateral slowing, dysrhythmia	Hypsarrhythmia	Hypsarrhythmia	-	-	-	Discrete localized changes in the left side and “generalized paroxysmal seizures”	Mild to moderate generalized slow wave activity	Normal background activity, during sleep remarkable period of 20 s duration with theta-delta activity 3-4 Hz	-	Generalized spike-wave			

FIAS, focal impaired awareness seizures; GTC, generalized tonic-clonic.

with a genetic abnormality was a boy with *TSC1* mutation [Hansen et al., 2016].

As this is an isolated case, there is a considerable likelihood that the finding of torpedo maculopathy was coincidental; however, ophthalmological abnormalities are commonly reported in *NEXMIF* pathogenic variant carriers. The most common eye problem is strabismus, reported in 7 out of 15 affected males (47%) [Cantagrel et al., 2004; Van Maldergem et al., 2013; Lambert et al., 2018; Lorenzo et al., 2018]. Additionally, Lorenzo et al. [2018] presented a male with a *NEXMIF* pathogenic variant who has keratoconus. We also reviewed the 24 published females with *NEXMIF* pathogenic variants for reports of eye abnormalities and found 2 patients with esotropia [Webster et al., 2017]. Our patient had a mild astigmatism in addition to torpedo maculopathy. Taken together, these clinical reports suggest that *NEXMIF* may play a key role in ocular development, though females with hemizygous pathogenic variants may have protection conferred by their normal allele.

From a developmental perspective, our patient's motor delays are milder than the vast majority of patients reported previously. He walked unaided at 18 months, whereas the mean age of walking for reported male patients is 39.2 months (range 17–72; 16.9 SD). Additionally, previously reported patients have been described with prominent dysmorphic features, including round face, narrow foreheads, anteverted nares, and long ears, features which were not present in our patient [Cantagrel et al., 2004; Van Maldergem et al., 2013; Kuroda et al., 2015]. Instead, he has only a bulbous nose and upslanting palpebral fissures. Moreover, our patient does not have microcephaly, hypotonia or growth retardation, features that are frequently reported in males with *NEXMIF* pathogenic variants [Cantagrel et al., 2004; Van Maldergem et al., 2013].

Although both males and females with *NEXMIF* mutations suffer from ID and autistic behavior, male patients have more severe ID [Van Maldergem et al., 2013; de Lange et al., 2016; Shirley et al., 2018]. In contrast, the most common clinical finding in females is epilepsy. Twenty-one out of 24 affected females are reported to have seizures, whereas this number drops to 6 out of 15 in male patients [Athanasakis et al., 2014; Moysés-Oliveira et al., 2015; de Lange et al., 2016; Farach and Northrup, 2016; Webster et al., 2017; Lambert et al., 2018; Samanta and Willis, 2018]. Our patient had no convincing history for seizures, but generalized epileptiform activity was seen on EEG. This finding confirms that the epilepsy phenotype in patients with *NEXMIF*

pathogenic variants is almost always generalized in nature, and that the EEG signature may be present in the absence of clinical seizures.

Recently Lorenzo et al. [2018] described cutaneous findings as multiple café-au-lait spots and cutaneous mastocytosis in 2 males. Similarly, we noted 1 large café-au-lait spot in our patient who has no family history of neurocutaneous syndromes. Thus, careful skin examination of the patients who have *NEXMIF* pathogenic variants is warranted.

Previously, Cantagrel et al. [2004] presented positive MRI findings in 2 males who have *NEXMIF* pathogenic variants. One of them had moderate brain atrophy, enlarged ventricles, and thin corpus callosum, whereas the other one had a small brain with mild enlargement of sulci in the frontal lobes. Our patient has enlarged extra-axial spaces in the frontal regions as well, emphasizing that mild-moderate cerebral atrophy is a relatively early MRI finding.

In conclusion, the presented patient expands and clarifies the phenotypic spectrum which may be seen in association with *NEXMIF* pathogenic variants. All patients with *NEXMIF* pathogenic variants should be referred to ophthalmology as subtle deficits may be difficult to identify in patients with developmental impairment. The finding of epileptiform discharges on EEG does not necessarily mean antiepileptic treatments are needed.

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Statement of Ethics

Informed written consent was obtained from the patient's parents. This study was approved by the McGill University Health Centre Research Ethics Board (2018-3937).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Alarcon-Martinez reviewed the patient's history and medical chart, conducted a literature review, and drafted the initial manuscript. Dr. Khan reviewed and edited the manuscript. Dr. Myers supervised Dr. Alarcon-Martinez in the initial preparation of the manuscript, prepared the figure, and reviewed and edited the manuscript.

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