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BRIEF COMMUNICATION

Novel *NEXMIF* pathogenic variant in a boy with severe autistic features, intellectual disability, and epilepsy, and his mildly affected mother

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Abstract

Intellectual disability (ID) and autism spectrum disorders are complex neurodevelopmental disorders occurring among all ethnic and socioeconomic groups. Pathogenic variants in the neurite extension and migration factor (*NEXMIF)* gene (formerly named *KIAA2022*) on the X chromosome are responsible for ID, autistic behavior, epilepsy, or dysmorphic features in males. Most affected females described had a milder phenotype or were asymptomatic obligate carriers. We report here for the first time mother-to-son transmission of a novel *NEXMIF* truncating variant without X-inactivation skewing in the blood. Truncating gene variant leads to symptomatic mother to severely affected son transmission. Our findings emphasize that *NEXMIF* sequencing should be strongly considered in patients with unexplained autism spectrum disorder, ID, and epilepsy, irrespective of gender. Such testing could increase our knowledge of the pathogenicity of *NEXMIF* variants and improve genetic counseling.

Introduction

Intellectual disability (ID) and autism spectrum disorder (ASD) are complex neurodevelopmental disorders and are often intricately linked. Genetic factors play a major role in ID and ASD [1–4]. The neurite extension and migration factor gene (*NEXMIF*), formerly named *KIAA2022*, is located on the X chromosome and encodes for a nuclear protein, which plays a role in brain development [5–8]. Previous data demonstrated evidence for a causal association between the *NEXMIF* gene disruptive variants and ID, with or without the presence of ASD and epilepsy (MIM 300912) [7–17]. Previously reported individuals with *NEXMIF* gene pathogenic variants showed that most males were severely affected, while most females had a milder phenotype or were asymptomatic. This is consistent with X-linked inheritance as the expression of X-linked traits are highly variable in females due to a number of mechanisms [18, 19].

In this study, we report a novel *NEXMIF* truncating variant in a family with a severely affected hemizygous son, who inherited from a heterozygous mildly affected mother. To our knowledge, this is the first report of symptomatic mother-to-son transmission with a documented X inactivation profile.

Case report

A 29-year-old woman (patient II, Fig. 1) was referred to the genetic-psychiatry outpatient clinic at Geneva University Hospitals (Geneva, Switzerland) for genetic counseling. She was born to a healthy mother (patient I, Fig. 1) in the

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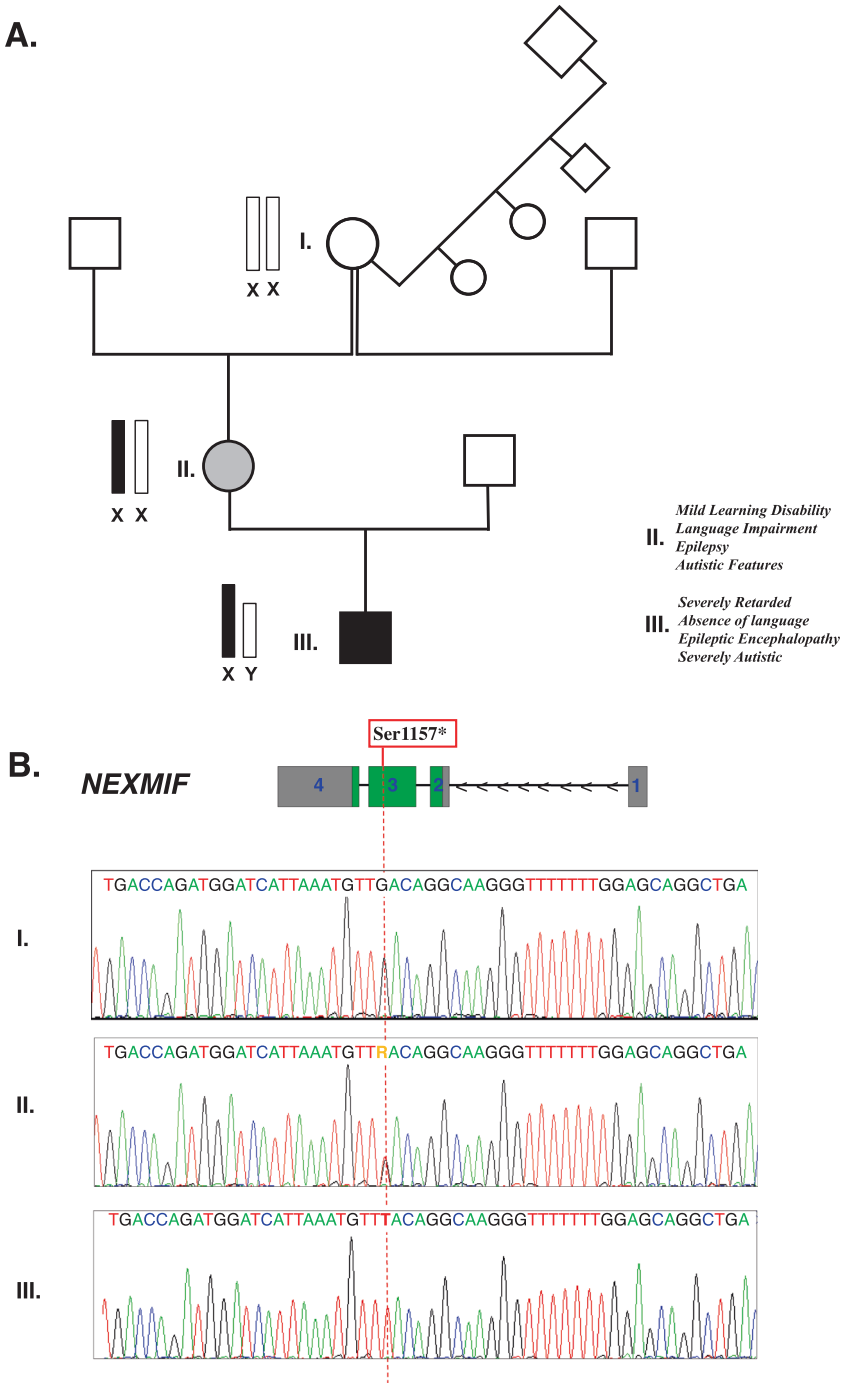

Fig. 1 **a** Family pedigree. Gray: female patient, milder phenotype. Black: male patient, severe phenotype. **b** Schematic representation of the variant in exon 3 of *NEXMIF* gene in patients II and III. Gray boxes correspond to non-coding sequences; green boxes correspond to coding sequences. Sanger sequencing chromatogram (red dashed line corresponds to the location of the variant)

Democratic Republic of Congo. Early childhood was unremarkable except for delayed language acquisition at 3 years of age and toilet training at 4 years of age. When she started school, major learning disabilities were observed. According to her mother, she presented with recurrent episodes of altered consciousness lasting for minutes, sometimes hours or days, from the age of 6 years, which were never investigated.

At 18 years, age of her arrival in Switzerland, she was slow in all tasks, presented with attention deficit, learning disabilities, and language impairment. She also showed behavioral features common to part of the ASD spectrum, such as strong intolerance to change and auto- and hetero-aggressivity. No dysmorphic features were observed, and brain magnetic resonance imaging was normal. She was tested for non-verbal cognitive abilities with the Wechsler Adult Intelligence Scale Third Edition (WAISIII), with a performance IQ of 47, corresponding to moderate ID. Verbal rating scales were not performed due to the language barrier. At 22 years, she presented with a first generalized

seizure and was briefly treated with valproic acid. At 28 years, she was readmitted with non-convulsive status epilepticus (NCSE), and valproic acid treatment was reinstated. In the context of poor compliance with a low drug level, she was admitted 18 months later with a second NCSE with intermittent myoclonic jerks. Treatment adjustment led to a rapid control of symptoms and the patient has remained seizure-free since then.

In 2009, patient II gave birth to a son born at term (patient III) after an uncomplicated pregnancy (birth weight, 3420 g [p25]; head circumference, 33 cm [<p3]; length, 51 cm [p10–p25]). He rapidly showed abnormal development with severe hypotonia, poor eye contact, inexpressive face, and severely delayed psychomotor milestones. At 6 months of age, he developed West syndrome and was treated initially by vigabatrin. Despite a significant reduction of spasms, he continued to exhibit variable seizure types during infancy, ranging from brief focal seizures with altered consciousness to myoclonic seizures and to late-onset spasms that were initially partially responsive to antiepileptic drugs (AED). At 2 years of age, the seizures gradually disappeared and allowed progressive AED withdrawal within 6 months. To date, there has been no seizure recurrence. Extensive metabolic investigations and brain magnetic resonance imaging were normal. He started walking at 4 years of age. He is now 7 years of age and shows auto- and hetero-aggressive behavior, absent speech, motor hyperactivity, poor attention span, limited interactions, and eye contact. He presents many stereotyped behaviors compatible with profound ID, together with autistic features. Formal developmental or cognitive assessment could not be undertaken. Minor dysmorphic features (hypertelorism and short philtrum), as well as a divergent strabismus, were noted on physical examination.

Methods

DNA was extracted from the blood of patients I, II, and III. Array Comparative Genomic Hybridization (CGH) was performed on patients I and II. Sequencing followed by targeted analysis of the coding and splicing regions of 1091 potentially causative genes was performed on patient II (Supplementary Table) and followed by Sanger sequencing on patients I, II, and III. Data were analyzed using UCSC genome Browser, GRCh37/hg19. X-chromosome inactivation (XCI) characterization was performed [20, 21].

Results

Exome sequencing on patient II allowed to identify a novel nonsense heterozygous variant in *NEXMIF* exon 3: NM_001008537.2:c.3470C>A:p.(Ser1157*). This variant is absent from the ExAC database and mutation databases (gnomAD, LOVD, ClinVar). However, it is classified as pathogenic according to the latest guidelines of the American College of Medical Genetics (class 5: PVS1, PM2, PM6) [22]. The variant was subsequently analyzed by Sanger sequencing in all three family members and showed a negative result in patient I, while patient III was a carrier (Fig. 1). Unfortunately, the father of patient III was unavailable for testing. No other clinically significant pathogenic variant was identified.

XCI analysis in the blood of patient II showed a methylation ratio estimated to be 64%:36%, considered as non-skewed [10]. In addition, CGH array enabled the detection of a 7p22.1 duplication in patients I and II (GRCh37/hg19), arr 7p22.1(5760,772–6,063,434) × 3 mat. From clinical characterization and the inherited character of the duplication, it was considered as non-pathogenic. There were no other clinically significant copy number variations.

Discussion

We describe a novel *NEXMIF* nonsense pathogenic variant, responsible for ID, autistic features, and epilepsy in a mildly affected mother and her severely affected son. This variant introduces a premature stop codon and we theorize that this leads to loss of function through nonsense-mediated mRNA decay. We assume that it appeared de novo in patient II as her mother does not carry the variant and her father was asymptomatic.

In males, several studies showed that the *NEXMIF* gene-disruptive variants can cause severe ID associated with epilepsy, autistic behavior, hypotonia, and subtle dysmorphic features. Most described females had a milder phenotype or were asymptomatic obligate carriers. Few females with a severe phenotype have been described, some with a skewed pattern of XCI in the blood [9–17]. This is consistent with X-linked transmission with variable expressivity [2, 10–17]. However, due to the lack of clinical data on unaffected female carriers, variability in the female phenotype remains difficult to explore.

Interestingly, as for *NEXMIF*, Doublecortin (*DCX*) gene mutations are responsible for X-linked ID and epilepsy. From a clinical and anatomical point of view, females are mildly affected and males are severely affected [23, 24]. Similar to *NEXMIF, DCX* plays a role in brain development and neuronal migration. *DCX*-mutated patients show phenotype variability, with a significant ratio of asymptomatic female carriers. For *DCX* and *NEXMIF*, phenotypic variability has been linked to X-inactivation mosaicism and somatic or germinal mosaicism, as well as skewed

X-inactivation [9–17, 19, 25, 26]. However, previous *NEXMIF* studies have reported that both males and females carrying truncating mutations were symptomatic, with males demonstrating more severe phenotypes [10, 11].

The pattern of inheritance in our case is compatible with X-linked transmission with variable expressivity. Our observation highlights that a truncating *NEXMIF* variant putatively leads to a severely affected son through transmission by a symptomatic mother, with a recurrence risk of 50% in both males and females. We emphasize that genetic testing, including *NEXMIF* sequencing, should be strongly considered for patients with ASD, ID, and epilepsy, irrespective of gender. When possible, XCI profiling, as well as the study of gene expression and mosaicism analysis, should be performed to increase the knowledge of the pathogenicity of *NEXMIF* variants and improve genetic counseling.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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