

A new gene mutation in a family with idiopathic infantile nystagmus

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Abstract:

Idiopathic infantile nystagmus (IIN) is an inherited disease, which can occur through a number of different inheritance patterns (autosomal dominant, recessive, or X-linked). The most common of these is X-linked inheritance with incomplete penetrance and variable expressivity, and can also be dominant or recessive. To date, only two mutations have been described: the first, affecting the FPR143 gene, which is associated with ocular albinism type I, and located on chromosome Xp22, and the second, affecting the FRMD7 gene located on chromosome X26-q27. To date, a causative gene on locus Xp11.3p11.4 has not yet been identified. The most common cause of IIN is due to mutations in the FRMD7 gene, located on chromosome Xq26. We present a case of a new mutation found in three siblings from a family with FRMD7-related infantile nystagmus, whose parents are consanguineously related in the first degree. A complex mutation has occurred in this family, which, to date, has not been previously reported in the scientific literature. The complex mutation consists of the presence of three consecutive 1 bp deletions in exon 12 (c.1248delT; 1299del C; and 1312delT), causing a secondary deletion (c.1340–2145 + 214del), and resulting in a truncated protein. We also present a 7-year-old patient from a different family, with periodic alternating nystagmus, having no mutation in the FRMD7 gene, which we assume may be an example of non-FRMD7-related IIN. This patient does not have a family history of nystagmus.

Keywords:

Idiopathic infantile nystagmus, motor nystagmus, periodic alternating nystagmus, sensory nystagmus

INTRODUCTION

In the past, nystagmus was classified as either sensory or motor. However, today, this classification is considered obsolete, as the term “motor nystagmus” is not entirely appropriate, given that every nystagmus, regardless of etiology, has a motor component.^[1,2] Similarly, “sensory Nystagmus” can be caused by an abnormality of the efferent visual system. Therefore, the authors such as Gottlob have proposed that “idiopathic infantile nystagmus” (IIN) or “idiopathic congenital Nystagmus” are more realistic classifications.^[1]

IIN is an inherited disease with an estimated prevalence of 2.4 cases per 10,000 inhabitants.^[3,4]

There exists a subset of patients among those with IIN whose condition is caused by a

mutation in the FRMD7 gene, located on the Xq26 chromosome. This form of IIN is termed FRMD7-related infantile Nystagmus (FIN).^[5] Individuals with IIN who have a family history consistent with X-linked inheritance may have an FRMD7 (FIN) mutation. Therefore, an individual who lacks a positive family history is more suggestive of having non-FRMD7 IIN (although there are rare *de novo* FRMD7 mutations).

We present a new FRMD7 gene mutation in a family of three siblings with FIN, whose parents are consanguineously related in the first degree. We also present another case of a 7-year-old girl from a different family, who exhibits periodic alternating nystagmus (PAN), and has no mutation in the FRMD gene and a negative family history of nystagmus. It is assumed that she may be an example of non-FRMD7 IIN, although the authors recognize the possibility that she could be a carrier of a hidden mutation from incomplete sequencing in the FRMD7 gene.

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CLINICAL CASES

Family 1

We present a family of three brothers with IIN. There is consanguinity in the first degree, and no other family history of nystagmus apart from the three brothers, who present with nystagmus since birth.

Patient 1

Male, 7 years of age with nystagmus since birth. He was born full-term, without complications, and exhibits normal psychomotor development.

On ophthalmological examination, his visual acuities (VA) are 20/30 in both eyes. Pupils are equal with normal reaction to light and accommodation.

The presence of conjugate horizontal pendular nystagmus is noted, with an eccentric null point on left gaze, resulting in an abnormal head posture (AHP) of a right face turn. The patient is orthophoric in the primary position.

Fundus examination shows a normal retina and optic nerve. Electroretinography (ERG) performed on this patient was unremarkable.

Patient 2

Male, 9 years of age, brother of patient's 1 and 3, who presents with nystagmus since birth without oscillopsia. He was born full-term, without complications, and exhibits normal psychomotor development.

VA are 20/30 in both eyes, with conjugate horizontal pendular nystagmus, and null point in primary gaze. The patient is orthophoric in the primary position.

Fundus examination shows a normal retina and optic nerve. ERG performed in this patient was unremarkable.

Patient 3

Male, 5 years of age, brother of patients 1 and 2, presents with nystagmus since birth without oscillopsia. He was born full-term, without complications, and exhibits normal psychomotor development.

VA are 20/50 in both eyes, with conjugate horizontal pendular nystagmus and null point in primary gaze. The patient is orthophoric in the primary position.

Fundus examination shows a normal retina and optic nerve. ERG performed on this patient was unremarkable.

GENETIC ANALYSIS

Genetic analysis of the above patients was performed using the following method: the 12 coding exons and the exon-intron boundaries of the FRMD7 gene (OMIM: *300628) on chromosome Xq26.2 were amplified by polymerase chain reaction (PCR) and sequenced directly. The resulting sequence data were compared with the reference sequence NM_194277.2. Deletion/duplication analysis of the FRMD7

gene was performed by applying multiplex ligation-dependent probe amplification (MLPA) using the Kit SALSA MLPA P269-A2 FRMD7. All coding exons except 3 and 10 of the FRMD7 gene and adjacent regions were screened for deletions/duplications.

The analysis shows that patients 1, 2, and 3 carry hemizygous deletions c. (1248delT; 1299delC; 1312delT; 1340–2145+214del) in exon 12 of the FRMD7 gene. Direct sequencing analysis did not detect any pathogenic sequence variants in exons 1–11 of the FRMD7 gene. However, PCR amplification of the exon 12 failed, repetitively, even with alternative primer pairs indicating a deletion of exon 12. Surprisingly, applying MLPA technique did not reveal any deletion of the FRMD7. Long-range PCR amplifying a region from c.1051–78 to c. 2145 + 977 encompassing 2150 bp is much shorter than would be expected from the wild-type sequence. Sequence analysis revealed three consecutive 1 bp-deletions: C.(1248delT; 1299delC; 1312delT), predicting an intermittent frameshift, and one gross deletion (c. 1340–2145+214del) resulting in a truncated protein. Interestingly, this large deletion in exon 12 does not affect the binding sites of the two independent MLPA-probes of exon 12, which explains the unexpected MLPA results. The gross deletion alone should have a deleterious effect on the FRMD7 protein sufficient to cause disease. It is possible though that the intermittent frameshift caused by the three 1 bp-deletions preceding the gross deletion alone would also elicit disease or at least contribute to it. In summary, the identified aberrations may be considered a complex mutation allele.

FAMILY 2

Patient 4

Female, 7 years of age, who presents with nystagmus from the 1st months after birth, but which has increased since 2 years of age. She was born full-term, without complications, and exhibits a normal psychomotor development. There is no family history of nystagmus and her parents are not consanguineously related.

Upon ophthalmological examination, VA is 20/50 in both eyes and pupils are equal with normal reaction to light and accommodation. Ocular alignment in primary gaze shows a small Exophoria.

The presence of conjugate horizontal jerk nystagmus is noted, where the fast-phase amplitude and direction is time dependent, alternating between cycles of jerk nystagmus with a fast-phase direction to the right, followed by cycles of jerk nystagmus with a fast-phase direction to the left. During the cycles, the jerk nystagmus progressively increases until reaching a maximum amplitude, after which it progressively decreases until disappearing completely for a few seconds, upon which a new cycle of jerk nystagmus in the opposite direction begins. The duration of the cycle is approximately 90 s. This is compatible with periodic alternating nystagmus (PAN). Likewise, the patient adopts an AHP with a face turn to the left or right depending on the phase of the PAN [Video 1].

Fundus examination shows a normal retina and optic nerve. Neurological examination and brain magnetic resonance imaging show no abnormality. ERG performed on this patient was unremarkable. Genetic analysis of this patient showed no mutation in the FRMD7 gene.

DISCUSSION

In this article, we present a new FRMD7 mutation in a family of three brothers with FIN (patients 1, 2, and 3), whose parents are consanguineously related in the first degree. The three brothers are 5, 7, and 9 years old and all present with congenital nystagmus without oscillopsia, as well as preserved VA ranging from 20/30 to 20/50.

The pendular nystagmus showed similar characteristics for each patient. The only difference being that for patients 2 and 3, the null point was in primary gaze, whereas patient 1 presented with an eccentric null point on left gaze, resulting in an AHP of a right face turn.

We also present a 7-year-old from a different family who exhibits PAN (POA) and has no mutation in the FRMD7 gene. We assume that this is an example of non-FRMD7 IIN, as there was no family history of nystagmus.

IIN is an inherited disease, which can occur through a number of different inheritance patterns (autosomal dominant, recessive, or X-linked). The most common of these is X-linked inheritance with incomplete penetrance and variable expressivity, and can also be dominant or recessive.^[6,7]

Specifically, in patients with IIN, the following loci have been located on chromosomes Xq26-q27, Xq22 y Xp11.3-p11.4.^[6,7]

To date, only two mutations have been described: the first, affecting the FPR143 gene, which is associated with ocular albinism type I, and located on chromosome Xp22, the second, affecting the FRMD7 gene located on chromosome X26-q27. To date, a causative gene on locus Xp11.3p11.4 has not yet been identified.^[8-12]

The most common cause of IIN is due to mutations in the FRMD7 gene, located on chromosome Xq26.

As for the genetic transmission of IIN, some studies mention that X-linked IIN is transmitted from female carriers to their affected children. Male-to-male transmission has not yet been described. Penetrance is complete in affected males but varies greatly among female carriers (20%–100%).^[13] This could be explained by the existence of skewed X-inactivation phenomenon, interaction with other genes, or even due to other nongenetic factors.^[14] This is consistent with the fact that no other members of our family are affected, other than the three brothers.

FIN is clinically characterized by two possible phenotype expressions:

- Horizontal, gaze-dependent (where the amplitude of the nystagmus increases on lateral gaze and decreases in primary position) conjugate pendular nystagmus
- POA.

In both the cases, nystagmus presents within the first 6 months of life. Binocular vision and color vision are usually well maintained, with relatively good visual acuity. Patients do not often complain of oscillopsia. An AHP can be seen in 15% of cases, secondary to an eccentric null point. There may also be an improvement of the nystagmus on convergence.^[5] In this respect, we can say that the patients from the first family coincide with the typical clinical features of FIN, highlighting the fact that only patient 1 has an eccentric null point.

The differential diagnosis of FIN is made primarily with patients who present with non-FRMD7 IIN. Such patients have similar characteristics, yet with certain peculiarities:

- Increased frequency of AHP and eccentric null points
- The amplitude of the nystagmus is not gaze dependent
- Pendular nystagmus is not as frequent, compared with those who have FIN.^[5]

In this respect, the clinical characteristics of family 2 (patient 4) differ greatly from family 1, where patient 4 presents clinically with PAN in the form of large horizontal jerk nystagmus with an amplitude and fast-phase direction being time dependent, alternating between cycles of jerk nystagmus to the right, and cycles of jerk nystagmus to the left. The duration of each cycle is approximately 90 s. Likewise, the patient adopts an AHP, alternating between left and right face turn, depending on the phases of the PAN.

With regard to the FRMD7 protein, it is a member of the FERM family (F for 4.1 protein, E for ezrin, R for radixin, and M for moesin), and therefore, within its composition, it has a FERM domain at its terminal position NH2.^[15] The FERM domain itself comprises three parts: FERM-N or N-terminal domain, FERM-M, and FERMC or C-terminal-acting binding proteins.^[16] Adjacent to the FERM domain is the FA (FERM-adjacent) domain, which functions to regulate the expression of neighboring FERM domains.^[12,17]

The FRMD7 protein is specifically expressed in the midbrain and hindbrain in embryos of 37 days, and it is thought that this protein may be involved in the development of the brain region responsible for the control of ocular motility.^[18,12]

It is hypothesized that the FRMD7 plasma protein exerts a function of organizing the interactions of membrane proteins with the cytoskeleton.^[19,20] This implies that FRMD7 mutations would ultimately cause a lack of regulation of neuronal growth in certain locations of the central nervous system which are keys to controlling ocular motility.^[21]

Approximately 43% of FRMD7 gene mutations are produced by the formation of a truncated protein causing a total absence of the same in affected males.^[22] However, up to 57% of patients present with a missense mutation,^[1] and it is thought that in these cases the disturbance in protein function would be responsible for the phenotypic expression.^[8]

In the first family described in this paper, a complex mutation occurred which has not been previously described in the

scientific literature to date. This complex mutation consists of the presence of three consecutive 1 bp deletions in exon 12 (c. 1248delT; 1299delC; 1312delT), causing a secondary deletion (c. 1340–2145 + 214del) and resulting in a truncated protein. Interestingly, this large deletion does not affect the binding sites of two independent MLPA-probes of exon 12. In this respect, Fingert *et al.* described a deletion in the FRMD7 gene in a family with IIN, which affected exons 2, 3, and 4.^[23]

Authors such as Gottlob have studied the effect of specific point mutations (c271Y, G24E, R229c, S340 L) in great depth, proving that the most damaging is the c271Y (which causes a nuclear kidnapping of the FRMD7 protein), whereas the most benign is the s340 L.^[1]

Until 2013, at least 48 mutations had been described.^[8,12] The majority of which were concentrated in the FA and FERM domains. This shows that both the domains are likely to play an important role in the function of the FRMD7 protein.^[12]

Patient 4 presents with no FRMD7 gene mutation, in contrast to the study by Thomas MG *et al.*, where 10 families and a singleton (21 patients in total) with PAN all carried some form of FRMD7 gene mutation.^[24]

Some authors have noted that some of the functions of the FRMD7 protein are closely linked to the CASK protein (from the MAGUK family), whose function is also involved in the development of neuronal processes or neurites.^[1] One of the specific functions of the CASK protein CASK is to recruit the presence of the FRMD7 protein in the cytoplasm where the most likely function of both in the growth of neurites is enhanced.^[1,25] As previously discussed, the FRMD7 protein once it is in the cytoplasm performs the function of remodeling the cytoskeleton, allowing the formation, elongation, and partition of axons and dendrites. Therefore, it is thought that the FRMD7-CASK cooperation allows for the formation of the neural network which is in charge of the control of eye movements.^[1,26] This explains why isolated mutations in both the FRMD7 gene and in the CASK protein can cause nystagmus.

X-linked intellectual disability is one of the syndromes specifically associated with CASK mutations, which can present with nystagmus as well as other manifestations such as cerebellar mental retardation, epilepsy, tremor, unsteady gait, and hypoplasia.^[27]

In conclusion, we present a family of 3 siblings with FIN, caused by a complex mutation of the FRMD7 gene not previously reported in the scientific literature, and resulting in a truncated protein. We also present another female patient from a different family who exhibits PAN, and has no mutation in the FRMD7 gene, which we assume could be an example of non-FRMD7 IIN. The authors recognize that she may be a carrier of a hidden mutation due to incomplete sequencing in the FRMD7 gene.

Declaration of patient consent

The authors certify that they have obtained all appropriate

patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed. Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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