Genotype and Phenotype Spectrum of FRMD7-Associated Infantile Nystagmus Syndrome

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PURPOSE. We investigate the genotype and phenotype spectrum of FRMD7-associated infantile nystagmus syndrome in Korean probands.

METHODS. A total of 37 patients with infantile nystagmus syndrome were recruited prospectively for genetic analysis. We performed polymerase chain reaction (PCR)-based direct sequencing and haplotype analysis for FRMD7. Detailed ophthalmic examinations and eye movement recordings were compared between FRMD7 and non-FRMD7 groups.

RESULTS. In 13 (35%) of 37 patients, five different mutations of FRMD7 were detected: start codon mutation c.1A>G, splice site mutation c.162+6T>C, and three missense mutations (c.575A>C, c.722A>G, and c.875T>C). The latter mutation was identified in seven unrelated patients, and always was accompanied with two single nucleotide polymorphisms of exon 12 (rs6637934, rs5977623). Compared to non-FRMD7 groups, a cup-to-disc ratio was significantly decreased in FRMD7 groups (P < 0.001), and a disc–macula distance to disc diameter ratio markedly increased in the FRMD7 group (P = 0.015). Most patients in the FRMD7 group had at least two types of the nystagmus waveforms, and the most common type was unidirectional jerk nystagmus (75%), such as pure jerk and jerk with extended foveation, followed by pendular (25%), bidirectional jerk (19%), and dual jerk (6%) nystagmus. No significant differences were observed between FRMD7 and non-FRMD7 groups in terms of the nystagmus waveform, presence of periodic alternating nystagmus, and mean foveation time.

CONCLUSIONS. We identified five FRMD7 mutations in 35% of our infantile nystagmus syndrome cohort, expanding its mutational spectrum. The missense mutation c.875T>C may be a common mutation arisen from the founder effect in Korea. Optic nerve dysplasia associated with FRMD7 mutations suggests that the abnormal development of afferent visual systems may affect neural circuitry within the oculomotor system.

Keywords: infantile nystagmus syndrome, FRMD7, founder effect, optic nerve head dysplasia

Infantile nystagmus syndrome (INS) is characterized by involuntary oscillation of the eyes, which is present at birth or manifesting within the first few months of life.1 It can be associated with visual system disorders, such as albinism, achromatopsia, and Leber congenital amaurosis, suggesting that the nystagmus may be sensory in origin. On the other hand, idiopathic IN (IIN) arises independently of any ocular or neurologic abnormalities. This has led to speculation that IIN may be caused by abnormal development of the ocular motor system itself rather than the afferent visual pathway.2,3

INS is a genetically heterogeneous disorder. To date, more than 100 genes have been associated with INS and there is significant overlap in phenotypic characteristics.3–5 IIN may be inherited as an autosomal dominant, autosomal recessive, or X-linked trait.6 The most common form of inheritance is X-linked, which can be dominant or recessive. Three X-linked loci have been reported at Xp11.4-p11.3, Xp22, and Xq26-q27. In 2006, Tarpey et al.7 first identified pathogenic mutations in FRMD7 located at Xq26. Approximately 50% of families with IN have been linked to the FRMD7 locus. Many studies revealed that FRMD7 protein is expressed mainly in the developing ocular motor structures, such as the cerebellum and vestibular nucleus, and has an important role in control of eye movement and gaze stability.7–9 However, recent studies using optical coherence tomography (OCT) demonstrated that individuals with FRMD7 mutations had abnormal retinal developments, including foveal hypoplasia and optic nerve head abnormalities.10 These raise a possibility that arrested retinal develop-
ments may be the underlying etiology in the development of nystagmus in INS.

We performed molecular genetic analysis on FRMD7 in a Korean cohort with INS to identify the causative mutations. We also investigated the ophthalmic and oculomotor characteristics of patients with FRMD7 mutations to elucidate the phenotype of FRMD7-associated INS.

METHODS

Patients

We prospectively recruited 37 unrelated Korean patients (19 men, 18 women, age range 9–67 years, mean ± SD = 43.5 ± 15 years) with INS from the Neuro-ophthalmology Clinic of two university hospitals in Korea. INS was defined as conjugate oscillations of the eyes with onset within the first 6 months of life. Other congenital forms of nystagmus, such as fusional maldevelopment nystagmus syndrome and spasmus nutans syndrome, were excluded. Of the patients, 13 had a family history of INS, and the remaining 24 were sporadic cases.

All experiments followed the tenets of the Declaration of Helsinki, and informed consent was obtained after the nature and possible consequences of this study had been explained to the participants. This study was approved by the institutional review boards of two participating hospitals (Pusan National University Hospital [PNUH] and Pusan National University Yangsan Hospital [PNUYH]). Because our study included all consecutive patients during the research period, two previous reported families were included in this report.11

Clinical Assessments

A total of 41 patients, including four affected members within the family, received detailed ophthalmic examinations and eye movement recording. The ophthalmic examinations included best-corrected visual acuity (BCVA), color vision, and anterior segment observation with slit-lamp biomicroscopy. Visual acuity was measured using the Snellen chart and converted to logMAR units.

Eye movements were recorded binocularly using infrared movement recording. The ophthalmic examinations included best-corrected visual acuity (BCVA), color vision, and anterior segment observation with slit-lamp biomicroscopy. Visual acuity was measured using the Snellen chart and converted to logMAR units.

Molecular Structural Modeling of Missense Mutations

Structural modeling of wild type and mutants of human FRMD7 FERM domain comprising residues 1 to 282 was performed using I-TASSER. The crystal structure of FERM domain of human protein DAL-1 (PDB accession code: 2HE7) having 40% sequence identity was used as a template. The resultant PDB files were visualized by Pymol (available in the public domain at www.pymol.org).

Statistical Analysis

A Mann-Whitney U test was used to compare continuous variables (visual acuity, C/D ratio, DM:DD ratio, mean foveation time of nystagmus) between FRMD7 and non-FRMD7 groups.
### Molecular Genetic Results

The patient’s molecular findings are summarized in Table 1 and Figure 1A. Five different mutations were detected in 13 (35%) of 37 unrelated patients. Six patients had a family history of INS (Fig. 2). Four mutations were novel: start codon mutation c.1A>G (p.M1V), splice site mutation c.162+6T>C, and two missense mutations c.575A>C (p.H192P) and c.722A>G (p.K241R). The remaining one was reported previously: missense mutation c.875T>C (p.L292P). All mutations were not found in 150 healthy controls.

We detected c.1A>G of exon 1 in two unrelated families (F1 and 2). The mutation leads to loss of the primary start codon ATG for methionine, which is replaced by a triplet GTG for valine. The alternative in-frame start codon is not present around a mutation. This mutation also was detected in another affected member within each family. In F3, a splice-site mutation was found at the 6th nucleotide of the splice donor site on intron 2 (c.162+6T>C). The mutation also was detected in proband’s mother and absent in public databases. Human Splicing Finder (HSF) predicted that this mutation will break the splice site and make new splice sites resulting in four bases longer on exon 2. A missense mutation c.575A>C of exon 7 was identified in two unrelated families (F5 and 6). The mutation would result in amino acid substitution of histidine by proline at codon 192. Another missense mutation was c.722A>G of exon 8 in a sporadic case (S20), which changed a highly conserved amino acid lysine by glycine at codon 241. Both missense mutations were absent in public databases and predicted to be pathogenic by all three prediction tools. The last mutation was the known missense mutation c.875T>C, which was found in a Belgian family with IIN. In our cohort, this mutation was detected in seven patients, including one family (F4) and six sporadic cases (S2, S3, S4, S9, S10, and S15). It had a MAF of 0.003 in the 1000 Genomes Project and 0.00003 in the ExAC Browser, but was absent in in-house controls. It was predicted to be pathogenic by all prediction tools, and the mutated residue of leucine was highly conserved.

Haplotype analysis was performed in seven unrelated patients with the c.875T>C mutation (See Supplementary Table S1). In SNPs analysis, we could not establish any LD among the SNPs within FRMD7. Furthermore, the 5000 kb region around FRMD7 showed no LD. However, direct sequence analysis of FRMD7 revealed that the c.875T>C mutation always was observed with two SNPs of exon 12, including c.1403G>A (rs6637934, MAF = 0.066) and c.1535T>C (rs5977623, MAF = 0.259; Fig. 1A). These SNPs were not observed in patients with another FRMD7 mutations except for c.162+6T>C (Table 2).

### Protein Structural Modeling

Figure 1B shows the structural modeling of novel missense mutations (p.H192P and p.K241R). The H192 residue is located in the middle of the β-sheets within F3-FERM domain. Therefore, the p.H192P mutation is likely to destabilize the overall structure of FRMD7 by disrupting the core β-strand conformation. On the other hand, the effect caused by the p.K241R mutation is not clearly apparent because it is located at the end of the predicted β-strand. Moreover, the side chain of lysine (K) is structurally similar to that of arginine (R), which is structurally similar to that of arginine (R).

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Protein Change</th>
<th>Exon/Intron</th>
<th>Variant Effect</th>
<th>In Silico Prediction</th>
<th>Domain</th>
<th>Affected</th>
<th>MA</th>
<th>PhastCons</th>
<th>PROVEAN</th>
<th>MutationTaster</th>
<th>SIFT</th>
<th>Protein Structural Modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1A&gt;G</td>
<td>p.M1V</td>
<td>Exon 1</td>
<td>Start codon mutation</td>
<td>Neutral</td>
<td>FERM</td>
<td>III2</td>
<td>0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c.575A&gt;C</td>
<td>p.H192P</td>
<td>Exon 7</td>
<td>Missense mutation</td>
<td>Disease-causing</td>
<td>FERM</td>
<td>III5</td>
<td>1</td>
<td>0.0004*</td>
<td>0.972</td>
<td>0.000003†</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c.722A&gt;G</td>
<td>p.K241R</td>
<td>Exon 8</td>
<td>Missense mutation</td>
<td>Disease-causing</td>
<td>FERM</td>
<td>III2</td>
<td>1</td>
<td>0.0004*</td>
<td>0.972</td>
<td>0.000003†</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c.875T&gt;C</td>
<td>p.L292P</td>
<td>Exon 9</td>
<td>Missense mutation</td>
<td>Disease-causing</td>
<td>FERM</td>
<td>III6</td>
<td>0</td>
<td>0.0004*</td>
<td>0.972</td>
<td>0.000003†</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* MAF based on the 1000 Genomes Project.
† MAF based on the exome aggregation consortium (ExAC).
suggesting that the mutation from lysine to arginine in this residue might not significantly affect overall structure.

**Clinical Characteristics**

Detailed ophthalmic and oculomotor findings of patients with FRMD7 mutations are summarized in Supplementary Tables S2 and S3. Comparisons of clinical characteristics between patients with and without FRMD7 mutations are described in Table 3. In the FRMD7 group, the mean C/D ratio was below normal range (0.33 ± 0.15, normal 0.4 ~ 0.6), and significantly decreased compared to that in the non-FRMD7 group (0.51 ± 0.20, \( P < 0.001 \); Fig. 3), whereas the mean DM:DD ratio considerably increased in the FRMD7 group (3.04 ± 0.53) compared to the non-FRMD7 group (2.80 ± 0.37, \( P = 0.015 \)). Four patients in the FRMD7 group had morphologic changes of the optic nerve head, including segmental hypoplasia (II1 of F1 and III6 of F4) and peripapillary pigment (S15 and S20). None of the FRMD7 group patients had macular hypoplasia or anomalies of anterior segments. The FRMD7 group had a better visual acuity than the non-FRMD7 group, but there were no significant differences in color vision abnormalities and presence of strabismus between the groups.

The waveforms of nystagmus were classified into the 12 categories of pendular, jerk (uni- and bidirectional), and dual jerk waveforms. Most patients in the FRMD7 group had at least two types of waveforms. The most common type was unidirectional jerk nystagmus (75%), such as pure jerk and jerk with extended foveation, followed by pendular (25%), bidirectional jerk (19%), and dual jerk (6%) nystagmus. Two patients in the FRMD7 group had a PAN with a periodic (S2) or an aperiodic (S4) cycle. Foveation time ranged from 59 to 158 ms (mean ± SD = 100 ± 30 ms) in the FRMD7 group. No significant differences were observed between the FRMD7 and non-FRMD7 groups in terms of waveform of nystagmus (Fig. 4), presence of PAN, mean foveation time, nystagmus changes in darkness, and convergence effect for the nystagmus.

**DISCUSSION**

We identified five FRMD7 mutations in 35% (13/37) of our total INS cohort. Four of them were novel mutations. Interestingly, some unrelated patients had the same mutation, and the known mutation of p.L292P was found in 54% (7/13) of the FRMD7 group. In addition, the mutation detection rate of sporadic cases (7/24, 29%) was higher than that in other studies. Our study supported that FRMD7 mutations are the underlying pathogenesis of the molecular mechanism for INS.

The FRMD7 consists of 12 exons and encodes a 714-residue polypeptide.6,19 It contains a conserved N-terminal FERM domain and FERM-adjacent (FA) domain, whereas the C-terminal region has no significant homology to other pro-
The FRMD7 protein is expressed in the developing brain, which controls eye movements and gaze stability, and has been shown to involve regulation of neuronal cytoskeletal dynamics through CASK-induced or Rho GTPase signaling. Thus, FRMD7 mutations can cause abnormal eye movements and gaze instability. To date, over 70 different mutations within FRMD7 have been reported. Many mutations cluster around the F3 lobes of the FERM and FA domains. This suggests that these domains have important roles in the function of FRMD7. Three (p.H192P, p.K241R, and p.L292P) of our mutations are located in the F3 lobe and FA domain. The molecular structural modeling reveals that p.H192P mutation is likely to destabilize the overall structure of FRMD7 protein by disrupting the core β-strand conformation, but the effect of p.K241R mutation is not clearly apparent. Previously, p.L292P mutation, which is located in

**Figure 2.** Pedigree of six patients with FRMD7 mutations who had a family history of INS.

**Figure 3.** C/D and DM:DD ratio of the patients. Mean C/D (A) and DM:DD (B) ratios are significantly different between the FRMD7 and non-FRMD7 groups.
FRMD7-Associated Infantile Nystagmus Syndrome

Table 3. Comparisons of Clinical Characteristics Between FRMD7 and Non-FRMD7 Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FRMD7 group, n = 16</th>
<th>Non-FRMD7 group, n = 25</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, n (%)</td>
<td>10 (63)</td>
<td>13 (52)</td>
<td>0.453</td>
</tr>
<tr>
<td>Visual acuity, logMAR</td>
<td>+0.25</td>
<td>+0.75</td>
<td>0.051</td>
</tr>
<tr>
<td>Right eye</td>
<td>+0.21</td>
<td>+0.67</td>
<td>0.006</td>
</tr>
<tr>
<td>Left eye</td>
<td>+0.75</td>
<td>+0.67</td>
<td>0.006</td>
</tr>
<tr>
<td>Color vision abnormality, n (%)</td>
<td>1 (7)</td>
<td>2 (10)</td>
<td>0.775</td>
</tr>
<tr>
<td>Strabismus, n (%)</td>
<td>2 (15)</td>
<td>4 (18)</td>
<td>1.000</td>
</tr>
<tr>
<td>Anomaly of anterior segment, n (%)</td>
<td>0 (0)</td>
<td>8 (33)</td>
<td>0.015</td>
</tr>
<tr>
<td>Macular hypoplasia, n (%)</td>
<td>0 (0)</td>
<td>6 (29)</td>
<td>0.041</td>
</tr>
<tr>
<td>C/D ratio, mean ± SD</td>
<td>0.33 ± 0.15</td>
<td>0.51 ± 0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM/DD ratio, mean ± SD</td>
<td>3.04 ± 0.53</td>
<td>2.80 ± 0.37</td>
<td>0.015</td>
</tr>
<tr>
<td>Waveform of nystagmus, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pendular</td>
<td>4 (25)</td>
<td>7 (28)</td>
<td>0.564</td>
</tr>
<tr>
<td>Unidirectional jerk</td>
<td>12 (75)</td>
<td>25 (92)</td>
<td>0.147</td>
</tr>
<tr>
<td>Bidirectional jerk</td>
<td>3 (19)</td>
<td>4 (16)</td>
<td>0.569</td>
</tr>
<tr>
<td>Dual jerk</td>
<td>1 (6)</td>
<td>1 (4)</td>
<td>0.634</td>
</tr>
<tr>
<td>PAN, n (%)</td>
<td>2 (16)</td>
<td>5 (20)</td>
<td>0.441</td>
</tr>
<tr>
<td>Foveation time of nystagmus, mean ± SD (ms)</td>
<td>100 ± 30</td>
<td>108 ± 39</td>
<td>0.429</td>
</tr>
<tr>
<td>Nystagmus change in darkness, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation</td>
<td>0 (0)</td>
<td>4 (20)</td>
<td>0.124</td>
</tr>
<tr>
<td>Suppression</td>
<td>6 (38)</td>
<td>8 (40)</td>
<td>0.832</td>
</tr>
<tr>
<td>No change</td>
<td>6 (38)</td>
<td>7 (35)</td>
<td>0.943</td>
</tr>
<tr>
<td>Directional change</td>
<td>4 (25)</td>
<td>1 (5)</td>
<td>0.414</td>
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<tr>
<td>Nystagmus change during convergence, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td>0.483</td>
</tr>
<tr>
<td>Suppression</td>
<td>9 (60)</td>
<td>8 (62)</td>
<td>0.713</td>
</tr>
<tr>
<td>No change</td>
<td>3 (20)</td>
<td>4 (31)</td>
<td>0.427</td>
</tr>
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</table>

the FA domain was predicted to lead to change in α-helix conformation of the FA domain due to lack of a hydrogen on the amino group of proline and can also affect the recognition specificity of the hydrophobic ligands. However, these structural predictions must be verified using X-ray crystallography.

Among our mutations, the p.L292P mutation accounted for more than 50% of total patients with FRMD7 mutations. All patients carrying the p.L292P mutation came from the same restricted region (Gyeongsangnam-do) of Korea and shared common SNPs (rs6637934, rs5977623) of exon 12 within FRMD7, c.1403G>A (rs6657934) of two SNPs is a relatively rare variant with a MAF of 0.066, and also has been detected in another Korean INS family with the p.L292P mutation. These findings suggest that the p.L292P mutation might have arisen from the founder effect. The size of the shared haplotype may be small, because SNP analysis did not show LD around FRMD7. Historically, Gyeongsangnam-do, which is located in the southeast region of Korea, had been a part of the Silla of Three Kingdoms period in ancient times. In this region, a population mixing with neighboring populations was not easy due to geographic position, and there is a distinctive dialect and lifestyle. The fact that other mutations (p.M14V and p.H192P) also were detected in two unrelated families supports this explanation.

FRMD7 mutation is known to be linked to idiopathic INS without any abnormalities in visual systems. Our patients with FRMD7 mutations also showed relatively good vision without anomalies of anterior segments and macular hypoplasia. This leads to the assumption that FRMD7 mutations cause a primary defect in regions of the brain responsible for ocular motor control. However, the FRMD7 group in our study had a small C/D ratio and high DM/DD ratio, suggesting morphologic changes within the optic nerve head. Previous studies with OCT revealed retinal and optic nerve changes, including a shallow foveal pit, increased central macular thickness, decreased peripapillary retinal nerve fiber layer thickness, and shallow optic nerve cup in INS patients with FRMD7 mutations. They demonstrated FRMD7 mRNA expressions in the developing human retina and optic disc. We also reported anomalous appearances of the optic nerve head using OCT in patients with FRMD7 mutations. Recently, FRMD7 expression has been localized in starburst cells of the retina to establish spatially asymmetric inhibitory inputs to direction-selective ganglion cells (DS cells) along the horizontal axis. The dysfunction of FRMD7 might contribute to the lack of the horizontal optokinetic reflex by loss of horizontal direction selectivity. These findings reflect that the abnormal development of afferent visual systems may be associated with FRMD7 mutations and could affect neural circuitry within the oculomotor system.

Few studies have systematically investigated the nystagmus pattern of patients with FRMD7 mutations. In our FRMD7 group, unidirectional jerk nystagmus was the most common waveform, while pendular nystagmus was less common (25%) than in previous reports (approximately 45%). There was intra- and interfamilial variability in the nystagmus waveforms, and the phenotypes were not affected by the type of mutation. Although PAN was observed in two patients with the p.L292P mutation, another patient with the same mutation had no PAN. Previously, idiopathic infantile PAN associated with other FRMD7 mutations has been reported. These findings are in accordance with those of previous reports supporting the phenotypic variability of FRMD7 mutations. Furthermore, we could find no difference in nystagmus characteristics between patients with and without FRMD7 mutations. This implied the complex mechanisms to generate various waveforms associated with INS, which include abnormal neural circuitry of the slow eye movement and gaze-holding systems. This could be explained by the effect of other modifier genes or environmental factors. Alternatively, FRMD7 mutation alone is insufficient to generate nystagmus, but cerebellar plasticity may amplify and shape nystagmus waveforms similar to the hypothesis of oculopatellar tremor. The learning process in the cerebellum can be variable and diverse among individuals. Indeed, a previous study using a functional MRI identified the decline of the cerebellum as a possible site of the ocular motor network involved in INS.

This study has potential limitations. We did not check the binocular visual acuity. It would be more likely to represent the BCVA than monocular visual acuity in patients with nystagmus. Furthermore, we did not perform quantitative approaches of foveal hypoplasia and optic nerve changes using OCT imaging. The quantitative OCT measurements can achieve analysis of afferent visual systems in much greater detail than fundus photography.

In conclusion, we identified five FRMD7 mutations in our INS cohort. In particular, the missense mutation c.875T>C may be a common mutation arisen from the founder effect in Korea. Our results expand the mutation spectrum of FRMD7 and provide molecular evidence for the underlying pathogenesis of INS. Optic nerve dysplasia associated with FRMD7 mutations suggested that the abnormal development of afferent visual systems may affect neural circuitry within the oculomotor system.
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References


FIGURE 4. Waveforms of the nystagmus. There are no significant differences in waveforms of nystagmus between the FRMD7 and non-FRMD7 groups. P, pendular; UDJ, unidirectional jerk; BDJ, bidirectional jerk; DJ, dual jerk.


