Phenotypical characteristics of idiopathic infantile nystagmus with and without mutations in FRMD7

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Idiopathic infantile nystagmus (IIN) consists of involuntary oscillations of the eyes. The familial form is most commonly X-linked. We recently found mutations in a novel gene FRMD7 (Xq26.2), which provided an opportunity to investigate a genetically defined and homogeneous group of patients with nystagmus. We compared clinical features and eye movement recordings of 90 subjects with mutation in the gene (FRMD7 group) to 48 subjects without mutations but with clinical IIN (non-FRMD7 group). Fifty-eight female obligate carriers of the mutation were also investigated. The median visual acuity (VA) was 0.2 logMAR (Snellen equivalent 6/9) in both groups and most patients had good stereopsis. The prevalence of strabismus was also similar (FRMD7: 7.8%, non-FRMD7: 10%). The presence of anomalous head posture (AHP) was significantly higher in the non-FRMD7 group (P < 0.0001). The amplitude of nystagmus was more strongly dependant on the direction of gaze in the FRMD7 group being lower at primary position (P < 0.0001), compared to non-FRMD7 group (P = 0.83). Pendular nystagmus waveforms were also more frequent in the FRMD7 group (P = 0.003). Fifty-three percent of the obligate female carriers of an FRMD7 mutation were clinically affected. The VA's in affected females were slightly better compared to affected males (P = 0.014). Subnormal optokinetic responses were found in a subgroup of obligate unaffected carriers, which may be interpreted as a sub-clinical manifestation. FRMD7 is a major cause of X-linked IIN. Most clinical and eye movement characteristics were similar in the FRMD7 group and non-FRMD7 group with most patients having good VA and stereopsis and low incidence of strabismus. Fewer patients in the FRMD7 group had AHPs, their amplitude of nystagmus being lower in primary position. Our findings are helpful in the clinical identification of IIN and genetic counselling of nystagmus patients.

Keywords: X-linked idiopathic infantile nystagmus; FRMD7; obligate carrier; clinical characteristics; eye movements

Abbreviations: AHP = anomalous head posture; IIN = idiopathic infantile nystagmus; OKN = optokinetic nystagmus; VA = visual acuity


Introduction

Nystagmus consists of involuntary to and fro eye movements and it can have a severe effect on vision and social function (Pilling et al., 2005). The onset of idiopathic infantile nystagmus (IIN) is usually in the first months of life. IIN is characterized by an absence of other ocular
pathology such as albinism, congenital stationary night blindness or achromatopsia. Pharmacological and surgical treatments of IIN are just emerging (Hertle et al., 2004; McLean et al., 2007). In a recent survey of nystagmus in Leicestershire, UK, the prevalence of nystagmus has been estimated to be 2.4 in 1000 (Sarvananthan et al., 2006). IIN can be sporadic or hereditary. The most common mode of inheritance is X-linked and the gene has been localised on the long arm of chromosome X (NYS1) (Kerrison et al., 1998, 1999). We have recently found multiple mutations in a novel gene called FRMD7 (Xq26.2) (NYS1), which is a major cause of X-linked IIN (Tarpey et al., 2006) and has also been confirmed by others (Schorderet et al., 2007; Self et al., 2007; Zhang et al., 2007a, b).

Several families with nystagmus of autosomal dominant inheritance have been described in the literature (Allen, 1942; Dichgans and Kornhuber, 1964). Kerrison et al. (1998) localized a gene for autosomal dominant nystagmus (NYS2) to chromosome 6p12. Other loci for nystagmus with autosomal inheritance include NYS3 (MIM 608345) (Patton et al., 1993) and NYS4 (MIM 193003) (Ragge et al., 2003). Nystagmus of autosomal recessive inheritance (MIM 257400) has been described by Waardenburg in 1961.

There have been attempts in the literature to cluster different types of congenital nystagmus together, based on the waveforms obtained through eye movement recordings. Twelve characteristic waveforms have been described in congenital nystagmus (Dell’Osso and Daroff, 1975). Hertle and Dell’Osso (1999) proposed that infantile nystagmus is a single clinical entity regardless of associated sensory abnormalities.

There are only few published data on the clinical characteristics of IIN. In most published reports, all forms of infantile nystagmus have been pooled together as a single entity irrespective of the aetiology (von Noorden and La Roche, 1983; Hertle and Dell’Osso, 1999). Abadi and Bjerre in 2002 described the motor and sensory characteristics of 224 subjects with infantile nystagmus of various aetiologies. He classified infantile nystagmus into three categories, i.e., idiopathic, associated with albinism and due to other causes and did not find differences in waveforms.

The detection of FRMD7 allows, for the first time, the analysis of a large group of IIN patients, where the cause of disease is homogeneous. In this study we describe the clinical and eye movement characteristics of 90 subjects with IIN due to mutations in FRMD7 and 48 subjects with IIN not caused by mutations in FRMD7. In addition, eye movement recordings of unaffected obligate female carriers of mutations in the FRMD7 gene are analysed.

**Patients and Methods**

This work is based on a previous study in which we found mutations in the FRMD7 gene in 23 families with X-linked IIN (Tarpey et al., 2006). We identified 90 subjects with IIN due to mutations in FRMD7 gene (mean age 36 years and range 3–88 years). Of these 90 subjects in the FRMD7 group, 88 had familial nystagmus whilst two were sporadic. The phenotypes of these subjects were compared to 48 subjects with IIN not caused by mutations of this gene (mean age 29 years and range 4–79 years). Of the 48 subjects in the non-FRMD7 group, 33 were sporadic, whilst the remaining 15 had at least two affected members in the family. Affected males and females were compared to see if there were any differences in clinical features and eye movements. Eye movement recordings were obtained in 52 affected subjects in the FRMD7 group and 29 affected subjects in the non-FRMD7 group.

We also identified and evaluated 27 obligate female carriers of FRMD7 mutations who were clinically unaffected comparing them to age matched healthy controls. In addition to the clinical data, eye movement recording were analysed in a subgroup of these unaffected carriers (n = 14), in particular to look for differences in smooth pursuit eye movements and optokinetic nystagmus (OKN).

Detailed ophthalmological examination was carried out on each subject. Slit lamp bio-microscopy was performed in the dark to rule out iris transillumination. The visual acuity (VA) was recorded using Snellen visual acuity charts. Binocular vision was examined using the Lang test. If the Lang test was positive, the Frisby test was used to investigate the level of stereopsis. Bagolini striate glasses were used when the Lang test was negative. Panel desaturated D15 and Ishihara’s chart was used to detect/ rule out colour vision abnormalities. The presence or absence of anomalous head posture (AHP) was analysed while patients were reading a distance visual acuity chart and was classified into three groups (No AHP: i.e. <5° of head turn, moderate: i.e. AHP of 5–15°, and large AHP: >15°).

Electro-diagnostic tests (electroretinogram and visual evoked potential to detect/rule out retinal disease and albinism) were done on all sporadic subjects and at least one member of each family from the familial subjects according to ISCEV standards (Marmor et al., 2004; Odom et al., 2004). All subjects and families with abnormal electrophysiology were excluded from the study.

Eye movements were recorded (250 Hz; EyeLink pupil tracker, SMI GmbH, Berlin, Germany) while viewing stimuli projected on a rear projection screen (1.8 x 1.2 m) using a video projector (Hitachi CP-X958). A 17” LCD monitor (Samsung SyncMaster 710 V) placed at a viewing distance of 40 cm was used during field trips. Each eye was calibrated separately offline by selecting foveations when fixating horizontal and vertical points at ±15° eccentricity and 0°. Visual tests were performed in horizontal and vertical directions including saccades (following targets from −20° to 20° in 10° steps moving every 1.5 s), smooth pursuit (20°/s velocity, ±20° amplitude: 10° and 40°/s velocities also performed if time permitted), OKN (20°/s velocity, square wave contrast gratings of 2.2° cycle size, Michelson contrast 0.88 cd/m²: 10° and 40°/s velocities also performed if time permitted) and steady fixation (up to 1 min recording at −15°, 0° and 15°).

Linear mixed models were used to statistically compare the effects of FRMD7 and non-FRMD7 inheritance including family, gender and eccentricity (for eye movements) as fixed factors excluding any non-significant interactions from the final models. Non-parametric data were either log transformed (i.e. amplitudes and frequencies) or analysed using Mann–Whitney U-tests (i.e. comparing VAs between FRMD7 and non-FRMD7 groups and also OKN and smooth pursuit eye movements of FRMD7 carriers to age-matched controls). The Pearson chi-squared test and the χ²-statistic were used to compare relative proportions between groups.
Results

Frequency of FRMD7 mutations

Mutations were detected in 15 of 16 (94%) families, which were linked to the NYS1 (Xq26-27) region and another 8 of 14 (57%) families in whom linkage data were not available (Tarpey et al., 2006). The eight family trees which were not shown in our previous publication are shown in Fig. 1.

VA and colour vision

In the FRMD7 group, the VA was tested in 83 of the 90 subjects. (We could not obtain accurate VA measurements in seven children.) Most of the subjects with mutations in FRMD7 had VAs better than logMAR 0.301 (Snellen equivalent 6/12) (Fig. 2, top panel). The median VA of this group was logMAR 0.176 (6/9) with upper and lower quartiles of logMAR 0.301 (6/12) and logMAR 0.097 (6/7.5), respectively.

In the non-FRMD7 group, VA was obtained in 45 of the 48 subjects, the data not being available in three children (Fig. 2, bottom panel). The VA distribution was similar to the FRMD7 group, the median being logMAR 0.176 (6/9) with upper and lower quartiles of logMAR 0.301 (6/12) and 0.0 (6/6), respectively. Mutations in the FRMD7 gene did not have any significant effect on VA of patients with IIN (Mann–Whitney U-test, \( P = 0.143 \)). Colour vision was normal in all the subjects from both groups.

In the FRMD7 group, there was a mild but significant difference in VA between affected males and females, the visual acuity being better in females (Mann–Whitney U-test, \( P = 0.014 \): median = 0.098 in females and 0.188 in males). In contrast, there were no significant differences between males and females in the non-FRMD7 group (Mann–Whitney U-test, \( P = 0.36 \): median = 0.176 in males and females).

Stereopsis

Of the 90 subjects in the FRMD7 group, 76 were tested for stereo-VA. Most of the subjects (93.4%) had good binocular vision demonstrable on Lang test. Seventy-one subjects who were Lang positive were examined using the Frisby test and were found to have a median stereopsis of 150". Of the five subjects who were Lang negative, four were Bagolini positive. The Bagolini negative subject had alternating esotropia. Six subjects with manifest strabismus detected on cover test were found to have binocular vision on Bagolini test.

In the non-FRMD7 group, 37 of the 48 subjects were checked for binocular vision. Twenty-nine subjects (78.4%) were Lang positive and their median stereopsis on Frisby test was also 150". Eight subjects were Lang negative, of which two were Bagolini positive. Pearson chi-squared test was used to compare the relative proportions of subjects who were Lang positive and showed a significantly higher proportion in the FRMD7 group (\( P = 0.019 \)).

Strabismus

Strabismus was detected in seven of the 90 subjects (7.8%) in the FRMD7 group. Three subjects had esotropia and three exotropia; one subject had left hypertropia. All the subjects (except one) with manifest strabismus had at least gross binocular vision (Bagolini positive). In the non-FRMD7 group, five of 48 (10.4%) had manifest strabismus,
all of them having esotropia (Pearson chi-squared test between the two groups, \(P = 0.61\)).

**Latent nystagmus**

None of the subjects from the FRMD7 group had latent nystagmus. However, one subject with strabismus in the non-FRMD7 group was found to have a latent component to the nystagmus.

**AHP**

We recorded head posture in 80 subjects in the FRMD7 group (Fig. 3). Sixty-eight of the 80 subjects (85%) did not have significant AHP, i.e. AHP \(<5^\circ\). Twelve subjects (15%) had AHP of 5–15°. None of the subjects in this group had vertical head posture and the horizontal AHP in this group never exceeded 15°. None of these subjects had had surgery for abnormal head posture.

Head posture was recorded in 45 of the 48 subjects in the non-FRMD7 group. Twenty-two of 45 (49%) did not have significant AHP, i.e. AHP \(<5^\circ\), whereas 11 subjects (24%) had moderate (5–15°) AHP. Twelve of the 45 subjects (27%) had AHP of \(>15^\circ\) of which eight subjects had undergone Kestenbaum procedure for AHP in the past. Of these 12 subjects with AHP \(>15^\circ\), four had vertical head postures (two chin down and two chin up). The comparison of the AHP in the two groups is shown in Fig. 3. Gamma statistic was used to compare the relative proportions between the groups and showed a highly significant difference between FRMD7 and non-FRMD7 groups (\(P = 5.7 \times 10^{-6}\)).
In the group with mutations in FRMD7, all subjects had conjugate horizontal nystagmus as well as most of the subjects in the non-FRMD7 group with the exception of two subjects who had conjugate vertical nystagmus. The amplitude, frequency and waveform of nystagmus varied considerably within families in both groups. Original eye movement recordings of subjects from a family which is representative of the FRMD7 group is shown in Fig. 4.

We evaluated the amplitude and frequency of nystagmus in three positions of gaze and the waveform of nystagmus in these positions were noted.

Amplitude of nystagmus
There was considerable intra- and inter-family variability in the amplitude of nystagmus. The amplitude of nystagmus in 15° left gaze, primary position and 15° right gaze of the subjects are shown in Fig. 5A. The mean amplitude (±SD) of nystagmus in primary position for males in the FRMD7 group was 3.86° (±3.52°), while the mean amplitude in the females was 3.27° (±2.44°). In the FRMD7 group, there was a reduction of amplitude in primary position of gaze with increase of amplitude in 15° gaze to the right and left, while no significant differences in amplitudes between primary position of gaze and eccentric position of gaze was found for the non-FRMD7 group (Fig. 5A, supplementary material: Fig. 1A). In the non-FRMD7 group, the mean amplitude of nystagmus in primary position was 5.76° (±3.89°).

In the FRMD7 group, gender (F = 0.03, P = 0.87) and family (F = 1.72, P = 0.09) were not significant predictors of log nystagmus amplitude, whereas eccentricity (F = 11.6, P = 2.9 × 10^-5) was highly significant. In contrast, eccentricity (F = 0.18, P = 0.83) was not a significant predictor of
log amplitude in the non-FRMD7 group. Gender ($F=3.35$, $P=0.07$) was also not a significant predictor of log amplitude in the non-FRMD7 group. The effect of eccentricity on amplitude can be clearly seen in Fig. 5A where a marked reduction in the mean log amplitude is evident at primary position ($0^\circ$) in the FRMD7 group but not in the non-FRMD7 group. Consequently, there was a significant difference in log amplitude between FRMD7 and non-FRMD7 groups at primary position ($F=7.29$, $P=0.009$) but not at $-15^\circ$ ($F=0.14$, $P=0.70$) or $15^\circ$ ($F=0.55$, $P=0.45$) eccentricity.

**Frequency of nystagmus**

The mean frequency of nystagmus in primary position was 4.08 Hz ($\pm 1.16$) for the FRMD7 group and 3.89 Hz ($\pm 1.24$) for non-FRMD7 group (Fig. 5B, supplementary material: Fig. 1B). Mean log of the frequency showed similar patterns in both groups (Fig. 5B). Eccentricity was not a significant predictor for log nystagmus frequency in either group ($F=1.86$, $P=0.16$ for FRMD7 and $F=0.44$, $P=0.65$ for non-FRMD7) (Fig. 5B). Log frequency of nystagmus was not dependent on gender ($F=0.007$, $P=0.93$ for FRMD7 and $F=1.11$, $P=0.30$ for non-FRMD7). There was no significant difference between the log frequencies of the FRMD7 group and non-FRMD7 group overall ($F=0.73$, $P=0.39$).

**Waveform characteristics**

The waveforms of nystagmus were compared with the 12 forms described by Dell’Osso and Daroff (1975) (Supplementary material: Fig. 2). The waveform varied with direction of gaze with some degree of intra- and inter-family difference. The frequency of pendular and jerk nystagmus was compared between groups using the Pearson chi-squared test. Pendular-related waveforms were more commonly associated with the FRMD7 group ($P=0.0025$; pendular waveforms account for 45.3% in FRMD7 group and 28.3% in the non-FRMD7 group).

**Obligate female carriers of a FRMD7 mutation**

Fifty-eight obligate female carriers were identified clinically. Female carriers were identified as unaffected when they were mothers or daughters of affected males who did not have nystagmus on clinical examination (slit lamp and fundus examination). Thirty-one (53.4%) of the 58 carriers, were affected clinically. As mentioned earlier, the only significant difference between the affected females and males was the slightly better VA in the females. The nystagmus characteristics (amplitude, frequency and the waveform) were similar in both the groups (affected females and males). We were able to obtain eye movement recordings of 14 clinically unaffected female obligate carriers of a FRMD7 mutation. Their mean age was 53.2 (range = 29–81). They were compared to 20 age-matched female control subjects who did not have any ophthalmological disease and were not related to subjects with nystagmus. They had normal Snellen VA (mean = 6/5). None of the carriers or controls had any strabismus or abnormal head posture. All of the carriers had normal stereo-acuity (Lang test). Eye movement recording of the clinically unaffected carriers revealed that one of them had sub-clinical nystagmus (amplitude 0.43° and frequency 2.86 Hz) (Tarpey et al., 2006).

Analysis of OKN in the unaffected obligate carriers showed a bimodal distribution, i.e. some of the carriers had good OKN gain, whilst the others had poor responses to optokinetic stimulus in most directions. An example of original eye movement recordings of OKN of a carrier and a control subject is shown in Fig. 6. This difference was significant for rightward (Mann–Whitney U-test, $P=0.03$) and downward ($P=0.002$) movement of the stimulus as shown in Fig. 7A. We also analysed horizontal and vertical smooth pursuit eye movements in clinically unaffected carriers and controls. There was no significant difference between the groups in the smooth pursuit gain and the number of catch-up saccades/second as shown in Fig. 7B ($P>0.05$).

**Discussion**

We detected mutations in 15 of 16 (94%) families with IIN, which were linked to the NYS1 (Xq26-27) region and in another 8 of 14 (57%) families in whom linkage data were not available (Tarpey et al., 2006). Mutations in FRMD7 are likely to be the major cause of inherited IIN and this finding has been shared by a number of recent publications. Schorderet et al. (2007) detected mutations in five of six families with X-linked IIN. Three of three Chinese families with congenital motor nystagmus were found to have mutations in FRMD7 (Zhang et al., 2007a) A large Turkish family was also reported to have mutations of the gene (Kaplan et al., 2007).

There are a few published studies in which the prevalence of these mutations was found to be lower. Zhang et al. (2007b) detected mutations in FRMD7 in 4 of 14 (28.5%) Chinese families with X-linked nystagmus. In another study from the UK, only 20% of the families with IIN were found
Nystagmus due to mutations in FRMD7

Fig. 7 (A) OKN gain of the obligate carriers and controls in the four directions of movement of the stimulus (leftward, rightward, upward and downward) moving at 20°/s. X-axis shows the two groups (carriers and controls), whilst the Y-axis depicts the OKN gain. OKN gain shows a bimodal distribution in the carriers especially in the leftward, rightward and downward gazes. (B) (i) Horizontal and vertical smooth pursuit gain in the obligate carriers and controls to stimuli moving at a linear velocity of 20°/s. X-axis shows the two groups (carriers and controls) and the Y-axis shows the smooth pursuit gain. In (ii) the number of catch up saccades per second is shown on the Y-axis.

to have mutations in the gene (Self et al., 2007). In our study, we examined several people from each family and if iris transillumination was detected in at least one subject, that family was excluded from the study to minimize the risk of including subjects with albinism, iris transillumination being one of the signs associated with ocular albinism. We believe that the utmost care taken in phenotyping has resulted in a higher prevalence of FRMD7 mutations in our study. In the singletons with IIN, we cannot be certain that we might have overlooked the possible subtle iris transillumination in some subjects, especially in children where the examination is difficult, possibly resulting in an apparent lower frequency of mutations (7%) of this gene.

We did not find a difference in most clinical and eye movement characteristics in patients with and without a mutation in FRMD7. Vision, stereopsis and ocular alignment was very good with a median VA of logMAR 0.176 (6/9) in both groups. However, the FRMD7 group had a significantly lower number of subjects with pronounced head turn and, correspondingly, had relatively smaller nystagmus amplitudes in primary position of gaze. Nystagmus waveforms showed large inter- and intra-familiar variation in both groups. However, pendular waveforms were significantly more common in the FRMD7 group. Affected females had similar clinical and eye movement characteristics as affected males except for VA, which was slightly better in females. In unaffected carriers we found subtle abnormalities in OKN.

The prevalence of strabismus in general population has been reported to be between 3% and 6%. Graham (1974) reported that the prevalence of strabismus is 5.66% based on a study done on 4784 children. 4.2% of 1187 children were found to have strabismus in a study done by Chew et al. (1994). In a study done in Denmark, the prevalence of strabismus was found to be 3.2% (Kvarnstrom et al., 2001).

Compared to the general population, the prevalence of strabismus in IIN has been reported higher in the previous literature. In a study by Forssman (1971), the prevalence of strabismus in IIN is reported to be 16%. He reported that more than one-third of the subjects with IIN had normal or near normal visual acuity. In another study (Brody and Fray, 1997), the prevalence of strabismus in IIN was reported to be 17%. Recently, Self et al. (2007) reported that the prevalence of strabismus is 44% in IIN due to mutations in FRMD7. However, this study was only based on nine affected subjects. Compared to these previous studies the prevalence of strabismus in our study was lower in the FRMD7 group (7.8%) and in the non-FRMD7 group (10%). These differences could be explained by the fact that patients with FRMD7 mutations are a homogeneous group. In addition, the lower prevalence of strabismus in our study may be partly attributable to our extensive examination of family members allowing better exclusion of patients with albinism and other eye diseases. The low incidence of strabismus in our study indicates that despite constant eye oscillations, subjects with IIN have good ability to fuse and so strabismus is only slightly more frequent compared to the general population (Chew et al., 1994; Graham, 1974). Subjects without associated strabismus had good stereo-acuity in both groups. The FRMD7 group had good stereovision more frequently (on the Lang test) than the non-FRMD7 group. This discrepancy could be explained by the observation that small squints are more difficult to measure on cover test and that stereovision might be a more sensitive measure for eye alignment in nystagmus.

It was interesting to note that none of the subjects in the FRMD7 group had latent nystagmus. However, one subject with strabismus in the non-FRMD7 group had a latent component to the nystagmus.

We found a median Snellen VA of 6/9 in subjects with IIN. Interestingly the VA in the two groups was very similar. We believe that we found a high level of VA because we carefully excluded other nystagmus forms such
as retinal diseases or albinism. Our study suggests that acuity below 6/18 (Fig. 2) should raise the suspicion of other underlying disease.

In their study on the clinical features of infantile nystagmus in the first 6 months of life, Hertle et al. (2002) have reported that 19% (five of 27 subjects) had an AHP. In a series by Abadi et al., nine of 16 (at least 53%) subjects (15 patients with IIN and one with albinism) were found to have AHP (Abadi and Whittle, 1991). We found that the prevalence of significant AHP was much less in the FRMD7 group than the non-FRMD7 group. This suggests that the null region of the nystagmus is central in subjects with FRMD7 mutations. However, the underlying anatomical basis of the null region characteristic of IIN is poorly understood. With in situ hybridization experiments we found that FRMD7 is expressed in the human cerebellum, the developing neural retina and the lateral ventricles (Tarpey et al., 2006). Possibly, these structures are involved in the formation of the null point position.

We found that there is intra- and inter-family variability in the amplitude and frequency of nystagmus in both the FRMD7 and non-FRMD7 group. Most of the waveforms described by Dell’Osso et al. were found in both groups. This is in accordance with the published literature. Kerrison et al. (1998) found that the waveform of nystagmus can differ in members of the same pedigree. Abadi et al. (1983) has reported dissimilar waveforms in monoyzotic twins with nystagmus. Hertle et al. (2005) published the clinical features of a family with periodic alternating nystagmus. He reported the presence of subclinical nystagmus in one member of the family in addition to the intra-familial variability of nystagmus.

The variable phenotype in subjects with FRMD7 mutations was not affected by the type of mutation. In this study, we have families with different types of mutations, i.e. truncating and missence mutations; however, the type of mutation did not predict the severity of clinical presentation. As in many other Mendelian disorders there is a high level of intra-familial variability of phenotype in our patients. This could probably be explained by the effect of other unlinked modifier genes and/or the effect of environmental factors. At present we are not sure if nystagmus is caused by a loss or gain of function of FRMD7.

We have shown that FRMD7 is expressed in the retina and cerebellum (Tarpey et al., 2006). It is interesting to note that patients with the mutations in this gene have good VA, suggesting that the retinal function is not severely affected. However, retinal involvement causative to nystagmus cannot be ruled out. The cerebellum has been associated with the neural integrator (Glasauer, 2003) and a number of acquired nystagmus forms (Leigh et al., 2002) and therefore it is plausible that cerebellar dysfunction related to the FRMD7 gene may be the pathology underlying IIN.

The penetrance of the gene was 53% among the carriers. It was interesting to note that one of the obligate carriers had sub-clinical nystagmus on eye movement recording. The basis of incomplete penetrance of this disease in females is currently not explained.

The optokinetic responses were subnormal in a subgroup of obligate carriers and this finding was not age related. However, smooth pursuit gain in obligate carriers and normal controls was similar. Smooth pursuit stimulus causing reversal of slow phase of nystagmus (Kelly et al., 1989) and inversion of optokinetic responses (Halmagyi et al., 1980) has been reported in patients with congenital nystagmus. In this context, absence of OKN response in these obligate carriers could be considered as a subtle subclinical manifestation of nystagmus. Eye movement recordings in obligate female carriers show a continuum between subjects having large amplitude nystagmus, small amplitude nystagmus, sub-clinical nystagmus, OKN abnormalities and normal eye movements.

In this article, we describe for the first time a clinical and eye movement analysis of a large homogeneous group of patients with nystagmus due to mutations in the FRMD7 gene, comparing them to a group of patients with IIN not due to mutations in this gene. The median VA was 6/9 in both groups and in patients with a visual acuity less than 6/18, suspicion of the nystagmus not being idiopathic should be raised. We also found good ocular alignment and binocular vision in patients with IIN. Interestingly, more patients in the non-FRMD7 group had AHPs and no decrease of nystagmus amplitude in primary gaze. We found that there is a wide variation of nystagmus waveforms even within families. Approximately half of the female carriers were clinically affected. However, some of the unaffected female carriers had subnormal OKN mainly in the horizontal direction. This most likely represents a sub-clinical affection of the eye movement system.

The clinical characteristics we have identified can be used to distinguish IIN from other forms of nystagmus, provide guidance as to what further investigations may be helpful, and assist in genetic counselling.

Supplementary material
Supplementary material is available at Brain online.

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