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Novel mutation c.980_983delATTA compound with c.986C>A mutation of the *FRMD7* gene in a Chinese family with X-linked idiopathic congenital nystagmus*

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Abstract: Objective: To screen mutations in FERM domain-containing protein 7 (*FRMD7*) gene in two Chinese families with X-linked idiopathic congenital nystagmus (XLICN). Methods: Common ophthalmic data and peripheral blood of two Chinese XLICN families (families A and B) were collected after informed consent. Genomic DNA was prepared from the peripheral blood of members of the two families and from 100 normal controls. Mutations in the *FRMD7* gene were determined by directly sequencing polymerase chain reaction (PCR) products. Results: We identified a novel mutation c.980_983delATTA compound with c.986C>A mutation in the 11th exon of *FRMD7* in family B, and a previously reported splicing mutation c.782G>C (p.R261G) in family A. The mutations were detected in patients and female carriers, while they were absent in other relatives or in the 100 normal controls. Conclusions: Our results expand the spectrum of *FRMD7* mutations in association with XLICN, and further confirm that the mutations of *FRMD7* are the underlying molecular mechanism for XLICN.

Key words: Mutation, Idiopathic congenital nystagmus, FERM domain-containing protein 7 (*FRMD7*)
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1 Introduction

Idiopathic congenital nystagmus (ICN) is primarily an oculomotor disorder characterized by bilateral involuntary, periodic, and predominantly ocular oscillations. The symptoms usually present at birth, or develop within the first three months of life. ICN has been found to be the most common type of nystagmus, and the prevalence of ICN is 1.9/10000 in Leicestershire and Rutland, UK (Sarvananthan *et al.*, 2009). Unlike "sensory defect nystagmus", ICN is independent of any other visual or neurological abnormality.

ICN may be inherited as autosomal dominant (OMIM 164100) (Patton *et al.*, 1993; Kerrison *et al.*, 1998; Klein *et al.*, 1998), autosomal recessive (OMIM 257400) (Tarpey *et al*., 2006), or X-linked (OMIM 310700) (Kerrison *et al.*, 1999; Tarpey *et al.*, 2006). However, the most common mode of inheritance is X-linked, which can be either dominant or recessive, and X-linked loci have been mapped to chromosomes Xq26–q27 (Cabot *et al.*, 1999), Xp22

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(Bassi *et al.*, 1995), and Xp11.3–p11.4 (Kerrison *et al.*, 1999). There are two genes that have been identified as disease-causing genes for X-linked ICN (XLICN). GPR143 maps to Xp22, and mutations within it are reported to cause ocular albinism type 1 (OA1), where nystagmus results as a secondary phenotype (Bassi *et al.*, 1995). Four-point-one ezrin, radixin, moesin (FERM) domain-containing protein 7 (*FRMD7*) resides at Xq26–q27, and mutations within it are approximately responsible for the 50% of ICN families (Tarpey *et al.*, 2006). However, there have been no responsible genes identified yet from the Xp11.3–p11.4.

In this study, we detected a novel mutation c.980_983delATTA compound with c.986C>A mutation in the 11th exon of *FRMD7* in a three-generation Chinese XLICN family B, and a previously reported splicing mutation c.782G>C (p.R261G) (Zhang B. *et al.*, 2007) in another four-generation Chinese XLICN family A. The mutations in *FRMD7* were detected in the patients and carriers, while it was not detected in other healthy family members or in the 100 normal controls. These findings expand on the spectrum of *FRMD7* mutations causing XLICN.

2 Materials and methods

2.1 Patients' data

Forty barley varieties were chosen for this study. Among these accessions, 12 are malting barley varieties released in recent years in China, and 28 are cultivated barley varieties collected from different countries, including the parental lines of several mapping populations and some commercial varieties imported to China as malt barley. Two XLICN families (families A and B) were recruited for this study from the Eye Center of the Second Affiliated Hospital of Zhejiang University, Hangzhou, China. Two patients (IV: 2, IV: 9), one carrier (III: 4), and one healthy member (IV: 10) from family A participated in the study (Fig. 1). Two patients (III: 1, III: 3), three carriers (II: 2, II: 4, III: 2), and two healthy members (II: 1, III: 5) from family B participated in the study (Fig. 1). Common ophthalmologic and orthoptic examinations were performed on all participants, including best corrected visual acuity in each eye, slit lamp biomicroscopy, fundus examination, ocular motor examination for strabismus, and binocular sensorial testing. Written consents were obtained from all participants according to the Declaration of Helsinki.

2.2 Genomic DNA preparation

Peripheral blood specimens (5 ml) were collected in an ethylenediamine tetraacetic acid (EDTA) coated vacutainer (Becton-Dickinson, Franklin Lakes, NJ, USA). We extracted genomic DNA in the peripheral blood leukocytes using a Simgen blood DNA mini kit (Simgen, Hangzhou, China).

2.3 Genetic analysis

The 12 exons and flanking intron sequences of *FRMD7* were amplified by the polymerase chain reaction (PCR), using previously reported primers

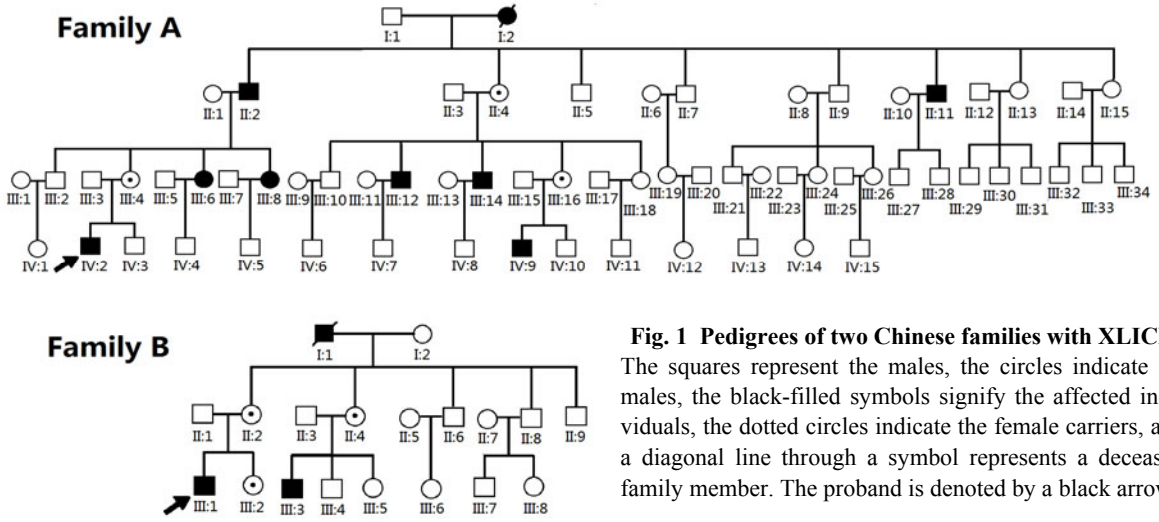

Fig. 1 Pedigrees of two Chinese families with XLICN
The squares represent the males, the circles indicate females, the black-filled symbols signify the affected individuals, the dotted circles indicate the female carriers, and a diagonal line through a symbol represents a deceased family member. The proband is denoted by a black arrow

(Du *et al.*, 2011; Hu *et al.*, 2012). PCR was performed in a volume of 25 μl in a DNA thermal cycler (Perkin Elmer, Norwalk, CT, USA) with primers listed in Table 1. PCR cycling conditions were as follows: 5 min at 95 °C, followed by 10 cycles of touchdown PCR with 1 °C reduction per cycle from 60 °C to 50 °C, followed by 30 cycles with denaturation at 95 °C for 30 s, annealing at 55 °C for 30 s, and extension at 72 °C for 45 s with a final extension step at 72 °C for 10 min. PCR products were isolated by electrophoresis on 1% agarose gels and sequenced using the BigDye terminator cycle sequencing kit V 3.1 (ABI Applied Biosystems; Sangon Co., China) on an ABI PRISM 3730 sequence analyzer, according to the manufacturer's instructions.

3 Results

3.1 Clinical findings

Two Chinese families with XLICN were analyzed. No male-to-male transmission was observed. The clinical data of the participants from families A and B are shown in Table 2. In the four-generation Chinese family A (from the Zhejiang province), eight of the sixty-five living family members are affected, including six males and two females. In addition, three females are obligate unaffected carriers. The proband of family A is a seven-year-old boy (family A, individual IV: 2) who has had nystagmus since four or five months after birth. He has a horizontal jerk ocular oscillation without head posture.

Table 1 Primers and PCR conditions for *FRMD7*

Exon	Forward primer (5′–3′)	Reverse primer (5′–3′)	Annealing temperature (°C)	Product size (bp)
1	CCTTGGGTGTGCATTACTTC	TTTGCTATTGTTGTCCCTTGAG	58	459
2	CGTGCTGCAGTATCAGGTTAG	CCCTACATACCTAGCTGCAAAC	58	243
3	TGACATTGCTGTTTGTTTCTACC	TCTCAAAGCCCTTTTCTCCC	60	304
4	GAGGGGACGGAAGAGGAGAGC	GGCATAACCCCCAAGTGGATAC	61	450
5	ATCTTGGATCTGGGAGAAGG	GCTTGGTTCTCTACCTGGC	58	238
6	GAGGACAAGGGTATGCTGGA	TCAGGTTTAAGGGCTTGCTC	58	281
7	GAGCTCTCAGGGTGGAAATG	ACACCCAAGTTTGAGCCAAG	58	293
8	GGCGGTCCCTCTCATTAAG	AAACGATTTGCAGAAACAACC	60	275
9	TTGGGATTTGAAGGTCTTTG	TCCTAAGCCTCCTGTGTTATTG	58	301
10+11	TTTAGTAGCCTATTGGTTTATGGC	TCAATTCATGGAAGCATTTG	58	401
12a	GAGGCTAATTTAGATCCCTCCC	CTGGCTTCATTGCAGTGGG	61	620
12b	TATGTGGACAAGCCACCCC	CTTCAGCAGTTGGTGTGTTG	61	613
12c	TGAATCAGAGATTCTTAAACCA	ACTGGGCCCCACACAAATAG	61	649

Table 2 Clinical findings of individuals in this study

Family	Individual	Age (year)	Gender	Age at onset	Best corrected visual acuity at presentation (logMAR unit)		Clinical finding
					OD	OS	
A	IV: 2	7	Male	4 or 5 months after birth	0.2	0.2	Horizontal oscillation without head posture
	IV: 9	26	Male	4 or 5 months after birth	0.1	0.1	Horizontal ocular oscillation with little head posture and head shaking
	IV: 10	24	Male	None	0.0	0.0	Normal
	III: 4	35	Female	None	0.0	0.0	Normal
B	III: 1	14	Male	Since birth	0.3	0.3	Horizontal ocular oscillation with face turn to right and the null point to the left
	III: 3	30	Male	Since birth	0.4	0.4	Horizontal ocular oscillation with little head posture
	II: 2	39	Female	None	0.0	0.1	Normal
	II: 4	42	Female	None	0.0	0.0	Normal
	III: 2	18	Female	None	0.0	0.1	Normal
	II: 1	43	Male	None	0.1	0.0	Normal
	III: 5	8	Female	None	0.0	0.1	Normal

logMAR: the logarithm of the minimum angle of resolution. OD: oculus dexter; OS: oculus sinister

The best corrected visual acuity of both eyes at distance is 0.2 [in the unit of logarithm of the minimum angle of resolution (logMAR)]. Another affected member of family A (IV: 9) is twenty-six years old with nystagmus since he was four or five months old. He has a horizontal ocular oscillation with little head posture and head shaking, and his best corrected visual acuity for both eyes is 0.1 (in logMAR unit). In family A, the penetrance appears to be complete in males and about 40% in females.

In the three-generation Chinese family B (from the Jiangxi Province), two males (III: 1, III: 3) of the eighteen living family members are affected. In addition, three females (II: 2, II: 4, III: 2) are obligate unaffected carriers. The proband of family B is a fourteen-year-old boy (family B, individual III: 1) who has had nystagmus since four or five months after birth. He has a horizontal jerk ocular oscillation, with face turn to right and the null point to the left. The corrected visual acuity of both eyes at distance with the comfortable head posture is 0.3 (in logMAR unit). His sister and mother are asymptomatic obligate carriers.

3.2 Mutation detected in *FRMD7*

Direct sequencing analysis detected a previously reported splicing mutation in family A, c.782G>C (p.R261G) (Zhang B. *et al.*, 2007), at the 9th exon of *FRMD7* in affected individuals (Fig. 2). This splice-site mutation results in substitution of the

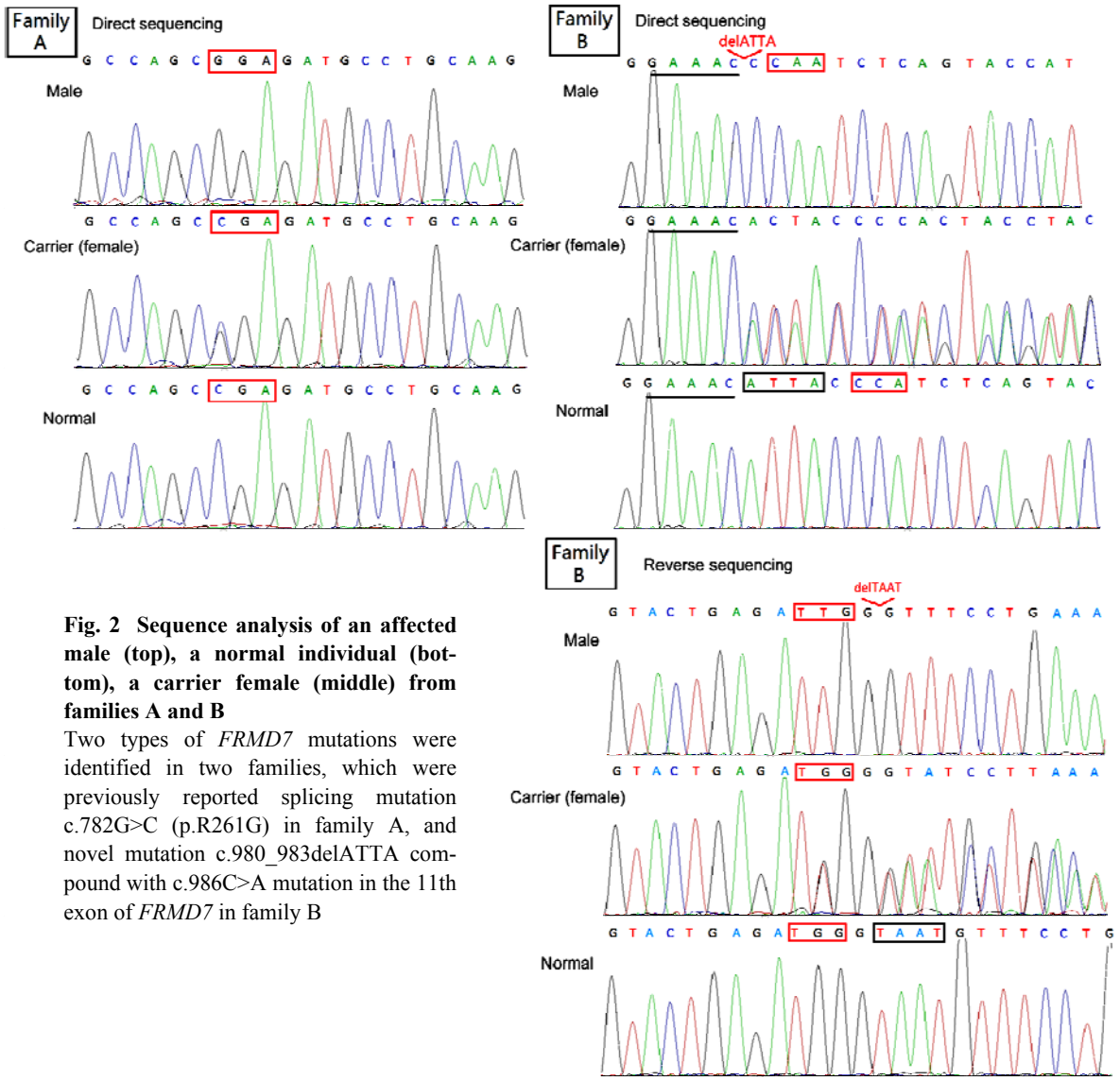

Fig. 2 Sequence analysis of an affected male (top), a normal individual (bottom), a carrier female (middle) from families A and B

Two types of *FRMD7* mutations were identified in two families, which were previously reported splicing mutation c.782G>C (p.R261G) in family A, and novel mutation c.980_983delATTA compound with c.986C>A mutation in the 11th exon of *FRMD7* in family B

arginine residue at codon 261 by a glycine residue (p.R261G). Direct sequencing analysis in family B detected a novel mutation c.980_983delATTA compound with c.986C>A mutation in the 11th exon of *FRMD7*. This mutation results in substitution of the proline residue at codon 329 by a glutamine residue (p.P329E) and a frame-shift at codon 327 and a putative stop codon 26 amino acids downstream in the translated protein (p.H327PfsX353). These two mutations were confirmed, and were further extended to other family members. These two mutations in *FRMD7* were not found in the unaffected members of the family or in the 100 unrelated controls.

4 Discussion

The human *FRMD7* gene comprises 12 exons spanning approximately 51 kb on chromosome Xq26–q27, and encodes a 714-residue polypeptide. *FRMD7* is a member of the super 4.1 family of proteins (Chishti *et al.*, 1998), and shares an FERM domain at its NH_2-terminus (Tarpey *et al.*, 2006) with band 4.1, ezrin, moesin, radixin, talin, filopodin, and merlin. The FERM domain of *FRMD7* is located between residues 2 and 282, and the FERM adjacent (FA) domain (FERM-adjacent region) is located between residues 288 and 336 (Fig. 3).

The FERM domain has a three-lobed 'clover-leaf' structure; each lobe represents a compactly folded structure. Lobe F1 (FERM-N, N-terminal FERM domain) has a fold resembling ubiquitin; lobe F2 (FERM-M) resembles acyl-CoA binding proteins; and lobe F3 (FERM-C, C-terminal actin-binding domain) has a fold related to pleckstrin homology domain/phosphotyrosine-binding domain (PTB) (Hamada *et al.*, 2000; Han *et al.*, 2000; Pearson *et al.*, 2000; Shimizu *et al.*, 2002; Smith *et al.*, 2003). The close packing of these domains suggests that they do not function independently, but rather form a co-ordinated structure (Baines, 2006). The conserved ezrin/radixin/moesin (ERM) proteins often organize membrane-cytoskeletal interactions (Tsukita and Yonemura, 1999), and share a C-terminal actin-binding domain and an N-terminal FERM domain that binds membrane proteins (Mcclatchey and Fehon, 2009), also acting as scaffolding for adaptor and signaling molecules (Mcclatchey and Fehon, 2009).

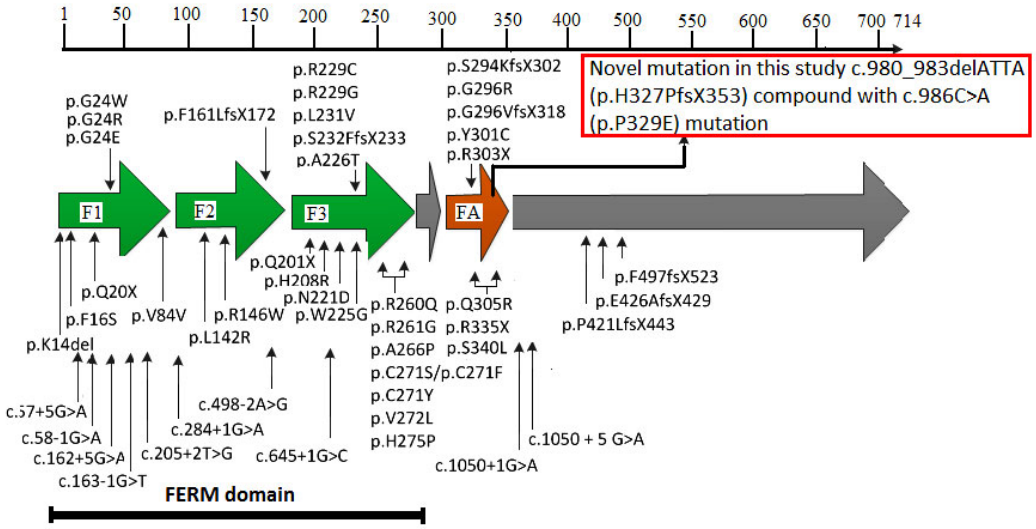

Fig. 3 Graphics of the FRMD7 protein

It consists of N-terminal FERM domain (green) and FERM adjacent (FA) domain (red). The FERM domain contains 3 lobes F1 (FERM-N), F2 (FERM-M), and F3 (FERM-C). The 48 positions of XLICN mutations have been reported previously (Tarpey *et al.*, 2006; Schorderet *et al.*, 2007; Self *et al.*, 2007; Shiels *et al.*, 2007; Zhang B. *et al.*, 2007; Zhang Q. *et al.*, 2007; He *et al.*, 2008a; 2008b; Kaplan *et al.*, 2008; Li *et al.*, 2008a; 2008b; 2011; Du *et al.*, 2011; Khan *et al.*, 2011; Thomas *et al.*, 2011; Hu *et al.*, 2012; Radhakrishna *et al.*, 2012) and the novel mutation in this study within *FRMD7* has been indicated (Note: for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article)

The FA domain is found next to the FERM domains, and defines a subset of FERM-containing proteins. The conservation of motifs in this region that are potential substrates for kinases, together with the known regulatory phosphorylation of 4.1R in this region, raises the possibility that the FA domain is a regulatory adaptation in this subset of the FERM proteins (Baines, 2006).

To date, 48 mutations in *FRMD7* have been reported worldwide in families with XLICN from various ethnic backgrounds (Fig. 3) (Tarpey *et al.*, 2006; Schorderet *et al.*, 2007; Self *et al.*, 2007; Shiels *et al.*, 2007; Zhang B. *et al.*, 2007; Zhang Q. *et al.*, 2007; He *et al.*, 2008a; 2008b; Kaplan *et al.*, 2008; Li *et al.*, 2008a; 2008b; 2011; Du *et al.*, 2011; Khan *et al.*, 2011; Thomas *et al.*, 2011; Hu *et al.*, 2012; Radhakrishna *et al.*, 2012). These mutations include missense, nonsense, splicing mutations, insertions, and deletions. Just under half of the mutations (43%) identified within *FRMD7* are predicted to cause gross defects at the protein level due to the introduction of frameshifts, nonsense mutations, and/or aberrant splicing. The other 57% of the mutations identified within *FRMD7* are missense mutations.

In the present study, we found a novel mutation, c.980_983delATTA compound with c.986C>A mutation, in a three-generation Chinese XLICN family B. The mutations in *FRMD7* were detected in the patients and carriers and were not detected in other healthy family members or in 100 normal controls. This supports that the identified mutations cause the pathogenesis of XLICN.

The novel mutation c.980_983delATTA (p.H327PfsX353) compound with c.986C>A (p.P329E) mutation locates at the 11th exon of *FRMD7* gene, and results in substitution of the proline residue at codon 329 by a glutamine residue causing a frameshift at codon 327 and a putative stop at codon 26 amino acids downstream in the translated protein in the FA domain of *FRMD7*. These two changes alter the length of the open reading frame, creating a *FRMD7* with an aberrant truncated FA domain. Since the FA domain is thought to be a regulatory adaptation in the FERM proteins, the aberrant truncated FA domain was considered to seriously affect the conservation of motifs in the FA region that are potential substrates for kinases, together with the known regulatory phosphorylation of 4.1R in this region. The FA region is immediately adjacent to FERM domains in all cases, is phosphorylated in vivo by protein kinase A (PKA) and protein kinase C (PKC), and regulates the activities of their neighboring FERM domain (Baines, 2006). FRMD7 protein expression may play an important role in regulating neuronal development, particularly in regions of the brain associated with ocular motor control (Betts-Henderson *et al.*, 2010). Therefore, the aberrant truncated FA domain caused by the novel mutation may induce XLICN by affecting the activities of the FERM domain protein.

The underlying molecular mechanisms for XLICN are not fully understood, but it is anticipated that the spectrum of *FRMD7* mutations will provide insights into this condition and the functioning and development of the visual pathways.

Our results expand the spectrum of *FRMD7* mutations in association with XLICN, and further confirm that the mutations of *FRMD7* are the underlying molecular mechanism for XLICN.

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We thank all the affected and unaffected family members that participated in our study.

Compliance with ethics guidelines

Feng-wei SONG, Bin-bin CHEN, Zhao-hui SUN, Li-ping WU, Su-juan ZHAO, Qi MIAO, and Xia-jing TANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the Ethics Committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University, China and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

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Genotype-phenotype correlations in Chinese patients with *TGFBI* gene-linked corneal dystrophy

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Abstract: In this paper, we report the clinical and molecular features of the distinct *TGFBI* (human transforming growth factor β-induced, OMIM No. 601692) gene-linked corneal dystrophy. Altogether, five pedigrees and ten unrelated individuals diagnosed as corneal dystrophy were recruited. Peripheral venous DNA was extracted, and then amplified by polymerase chain reaction (PCR) and scanned for mutation by single-stranded conformation polymorphism (SSCP). Direct DNA sequencing was used to analyze the mutations of the *TGFBI* gene. In our study, thirty patients from five pedigrees and ten sporadic patients were diagnosed as four *TGFBI* gene-linked corneal dystrophies of granular corneal dystrophy type I (GGCD I), Avellino corneal dystrophy (ACD), lattice corneal dystrophy type I (LCD I), and lattice corneal dystrophy type IIIA (LCD IIIA), and in total, seven disease-causing mutations, namely R555W, A546D, A546T, and T538P mutations in exon 12, R124H and R124C mutations in exon 4, and P501T mutation in exon 11, were identified, while four polymorphisms of V327V, L472L, F540F, and 1665–1666insC were screened in exons 8, 11, and 12. The study ascertained the tight genotype-phenotype relationship and confirmed the clinical and genetic features of four *TGFBI* gene-linked corneal dystrophies.