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Novel mutations of FRMD7 in Chinese patients with congenital motor nystagmus

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Abstract. The purpose of the current study was to identify novel mutations in the FRMD7 (FERM domain containing 7) gene and to characterize clinical features in Chinese patients with congenital motor nystagmus. For this purpose, 18 patients with congenital motor nystagmus were selected from the ocular genetic diseases bank of the Pediatric and Genetic Clinic of Zhongshan Ophthalmic Center (Guangdong, China). Direct sequencing was used to analyze the exons and adjacent introns of the FRMD7 gene. The heteroduplex-single strand conformation polypeptide method was used to analyze 96 unrelated normal controls and gene-screening positive patients. Slit lamp photography of the anterior segment, fundus photography, optical coherence tomography and electroretinogram were carried out to identify the clinical features of congenital motor nystagmus. The authors noted that in, 18 patients with congenital motor nystagmus, there were 7FRMD7 gene mutations (six new mutations). The screening rate was 38.89%, including c.41_43delAGA (p.13-15delK); c.473T>A (p.I158N); c.605T>A (p.I202N); c.580G>T (p.A194S); c.811T>A (p.C271S); c.1493insA (p.Y498X); c.57+1G>A (slice mutation). There were no such mutations in the 96 normal controls. These results enriched the gene mutation spectrum of FRMD7. The authors systematically investigated the clinical phenotype of congenital motor nystagmus in a Chinese population. The study provides further evidence for clinical diagnosis and differential diagnosis and genetic counseling.

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Introduction

Congenital nystagmus (CN) is a group of hereditary eye diseases, although the cause of the diseases has yet to be elucidated. It can be divided into sensory defective nystagmus and motor defective nystagmus according to its etiology. Sensory defective nystagmus can be originated from insufficiency image stimulus of macular region induced by the disease of anterior visual pathway, or the function loss of the fovea induced by organic diseases of macula, retina or optic nerve (1,2). Usually, sensory defective nystagmus can occur in a variety of diseases, such as congenital cataracts, aniridia, Peters' anomaly, oculocutaneous albinism, achromatopsia, cone rod dystrophy, macular defects, congenital stationary night blindness, Leber congenital amaurosis and optic nerve hypoplasia (1,2). Motor defective nystagmus may be originated from the central nervous system or the abnormal pathway controlling the eye movements. Patients with motor defective nystagmus don't have other ocular abnormalities (3,4). Congenital motor nystagmus (CMN), also known as congenital idiopathic nystagmus, is an isolated form of nystagmus, consisting of involuntary oscillations of the eyes. It is characterized by an absence of other ocular pathologies. A variety of genetic modes, such as autosomal dominant, autosomal recessive and X linked, have been proven to be associated with CMN (5-8).

In 1999, two X-linked CMN loci were reported, demonstrating that this form of inheritance is also genetically heterogeneous with a locus for X-linked irregularly dominant CMN, as reported by Kerrison *et al* (9) at Xq26-q27 (NYS1) and by Cabot *et al* (10) at Xp11.4-p11.3.8.

However, only one gene has been identified to be associated with X-linked CMN. In 2006, Tarpey *et al* (4) first identified nystagmus-causing mutations in the FRMD7 gene within the Xq26-q27 interval. In the present study, FRMD7 mutation analysis and detailed clinical evaluation were performed to identify novel mutations and characterize new clinical features of the Chinese population with CMN.

Materials and methods

Patients and clinical data. The patients presenting CMN were referred to the Pediatric and Genetic Clinic in the Eye

Hospital of the Zhongshan Ophthalmic Center (Guangzhou, China). Written informed consent was obtained from each participant prior to the study. The present study was approved by the Ethics Committee of the Zhongshan Ophthalmic Center (Guangzhou, China) and was performed according to the tenets of the Declaration of Helsinki. Medical and ophthalmic histories were obtained. A complete general physical examination and detailed ophthalmological examinations, including anterior segment observation with slit-lamp microscopy, fundus photography and optical coherence tomography, were conducted to identify the clinical features of CMN.

Mutation screening. Genomic DNA was prepared from venous blood. All of the primers (Takara Bio, Inc., Otsu, Japan) for FRMD7 (Table I) were used to amplify coding exons (exon1 to exon 12 of FRMD7) and the adjacent intronic sequence of the gene (NCBI human genome build 36.3, NC_000023.10 for gDNA, NM_194277.2 for cDNA and NP_919253.1 for protein of FRMD7). The PCR reaction was performed in a thermocycler (Biometra GmbH, Göttingen, Germany) under the following two conditions: The first was an initial denaturation at 94˚C for 5 min followed by 35 to 37 cycles of 94˚C for 30 sec, proper annealing temperature for 30 sec, and 72˚C for 30 sec with a final extension cycle of 72˚C for 5 min. The other condition was the touch down PCR program (Fig. 1). The PCR products of the exons and adjacent intronic sequences for the patients were sequenced with the ABI BigDye Terminator direct sequencing kit (version, 3.1; Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA) according to the manufacturer's recommendations and using a 3100 sequencer (Applied Biosystems; Thermo Fisher Scientific, Inc.) confirmed by the authors. Sequencing results from patients, as well as consensus sequences of FRMD7 from the NCBI human genome database (NM_001604.3) were imported into the SeqManII program of the Lasergene Package (DNASTAR, Madison, WI, USA) and aligned to identify variations. Each mutation was confirmed by bidirectional sequencing. Mutation was named according to the nomenclature recommended by the Human Genomic Variation Society.

Determination of changes in genetic information. The nucleotide sequences containing base variation and the standard sequences from NCBI human genome database were inputted into the MapDraw program of the Lasergene package to identify the impact of amino acid coding. Protein sequences of different species were identified from the NCBI website and entered into the MegAlign program of the Lasergene package, in order to compare the protein sequences of different species and estimate the conservation of mutation sites in the ClustalW program. The differences in amino acid changes and the possible pathogenicity of the mutation were evaluated through the Blosum 62 (http://www.uky.edu/Classes/BIO/520/BIO520WWW/blosum62.htm) and PolyPhen (http://genetics.bwh.harvard.edu/pph/) (11) analytical programs respectively.

Heteroduplex single-strand conformation polymorphism (SSCP) analysis. The variations detected in the gene were further evaluated in 96 normal controls (informed consent, in accordance with the Declaration of Helsinki, was obtained from the participating individuals before the study) by using heteroduplex-SSCP analysis as previously described in literature (12-14). DNA fragments of mutation sites were PCR-amplified according to Table I. PCR products were mixed with an equal volume of gel-loading buffer (95% formamide, 20 mM EDTA and 0.05% bromophenol blue, 0.05% xylene cyanol) and denatured at 95˚C for 5 min and immediately placed on ice for 5 min. The samples were loaded directly onto 8% polyacrylamide gels and run 8 h at room temperature at 40 W in a solution of 0.5X TBE (Takara Bio, Inc.).

Results

In 8 patients with CMN, there were 7 FRMD7 gene mutations (6 new mutations). The screening rate was 38.89%, including c.41_43delAGA (p.13-15delK); c.473T>A (p.I158N); c.605T>A (p.I202N); c.580G>T (p.A194S); c.811T>A (p.C271S); c.1493insA (p.Y498X); c.57+1G>A (slice mutation; Fig. 2).

The mutation identified in the present study resulted in a change at the protein level with a residue substitution weight by Blosum 62, and a 'probable damaging' effect identified by PolyPhen (Table II). The conservation of the protein in this position was identified by analyzing seven orthologs from different mammalian species (Fig. 3). These mutations were also investigated in 96 unaffected control individuals (Fig. 4) by heteroduplex-SSCP, but none were identified.

In the current study, all patients with idiopathic nystagmus were male. Nystagmus usually manifests as a midrange decline in visual acuity. The uncorrected visual acuity ranged from 0.1 to 0.4 and corrected visual acuity ranged from 0.4 to 0.9 (Table III). The results of customary slit lamp and fundus examinations were normal.

Discussion

CMN is an ocular motor disorder characterized by involuntary oscillation of the eyes that occurs in the first 6 months of life. It is speculated that the disease may be associated with the abnormal development of senior center monitoring the abnormal eye movements and eye gazing. The prevalence of CMN in the population is estimated to be 24 per 10,000 (15). It is known to be genetically heterogeneous as autosomal dominant, autosomal recessive and X-linked patterns of inheritance. X-linked inheritance with incomplete penetrance is the most common form (4-8). However, the majority of patients of CMN are sporadic cases.

Until now, FRMD7 is the only one gene that has been identified for X-linked CMN. It was demonstrated that FRMD7 expression is spatially and temporally regulated in the developing human embryonic cortex. FRMD7 is expressed in most adult human tissues, and has been detected in the developing neuroretina and regions of the embryonic brain known to control eye movement (16). FRMD7 consists of 12 exons and encodes a polypeptide with 714 residues polypeptide, spanning approximately ~51 kb on chromosome Xq26-q27. The FRMD7 protein has B41, FERM-N, FERM-M and FERM-C

Table I. Oligonucleotides used for FRMD7 amplification.

Exon	Sequences (5'-3')	Size of PCR products (bp)	Annealing temperature (°C)
FRMD7-exon1-f	AGGAAGTCCAGTTAGATTTG	428	58.7
FRMD7-exon1-r	ACAGTCCTCCTTCATTCAGT		
FRMD7-exon2-f	ATGCAGGTCCTCTAAACAGT	320	58.7
FRMD7-exon2-r	GGAATTGAACCCTACATACC		
FRMD7-exon3-f	GAAAATATAAGGGGGCAGAT	368	54.4
FRMD7-exon3-r	TGGATGTATGAAGGGTTGAA		
FRMD7-exon4-f	GAGGGGACGGAAGAGGAGA	287	61.6
FRMD7-exon4-r	TGAGAATGGCCAGAAGCACT		
FRMD7-exon5-f	CCCCAAAAAGGCATCTGA	339	57.3
FRMD7-exon5-r	TCTCCCCTGTAAACCCTAAC		
FRMD7-exon6-f	GATGGAGGACAAGGGTATGC	393	58.7
FRMD7-exon6-r	GCCACTGAAAGGGGAAAGAA		
FRMD7-exon7-f	AGCAAGCCCTTAAACCTGAG	391	58.7
FRMD7-exon7-r	CCCTTTCTGGCTGGTGATAA		
FRMD7-exon8-f	AATGCCTTCTTTGACCACAGC	365	62.9
FRMD7-exon8-r	GCCAGCCGGCTTTTACAAT		
FRMD7-exon9-f	AGTGGCCCTGTCTATTCCTC	551	62.9
FRMD7-exon9-r	GGTGCCCCCATCTTCCTC		
FRMD7-exon10, exon11-f	CTGCCTGGTCCTTGAATAAG	582	57.3
FRMD7-exon10, exon11-r	TCCCCAGGAAGCTAACCTA		
FRMD7-exon12a-f	ATGGATCTTGTTAAATGACTT	541	51.1
FRMD7-exon12a-r	ACCAACCTGCTGACCTGTA		
FRMD7-exon12b-f	TCCCACATTGCTACATCAGTC	520	58.7
FRMD7-exon12b-r	CAAATTTGGGTCTTCCTCTTC		
FRMD7-exon12c-f	ATGTGCCCTATATTCCTTGTA	592	58.7
FRMD7-exon12c-r	ATGGGTGACCTTATTTCTTTG		
FRMD7-exon12d-f	TCCCAGAGCCAATCAGACAT	435	58.7
FRMD7-exon12d-r	TTTCTGCCTAAGTCGGTAACA		
FRMD7-mutation (c.1403G>A/c.1492-1493intA)-f	CAAGCTGTAAGTTTTCTGGTAATC	213	[a]
FRMD7-mutation (c.1403G>A/c.1492-1493intA)-r	GACTTGTCCTTTCCTCTGCTC		
FRMD7-mutation (c.473T>A)-f	TGCTCCATTGCTAAGTTCCTCA	234	56.8
FRMD7-mutation (c.473T>A)-r	TCTGTCCCCAATTTTAGTGTTCTC		
FRMD7-mutation (c.605T>A)-f	CATTCTTGAGGCATTTATTAGG	173	[a]
FRMD7-mutation (c.605T>A)-r	GTGAGCAACAGCCAGGTGA		
FRMD7-mutation (c.580G>T)-f	GAGCTCTCAGGGTGGAAATGTCAT	246	61.1
FRMD7-mutation (c.580G>T)-r	GCTGAAGGGCTTGAAAGGAA		
FRMD7-mutation (c.811T>A)-f	GTTTGGAAGGCATTGGGATTTGAA	203	63.2
FRMD7-mutation (c.811T>A)-r	TTTGGGCTTTGATTTGGGCTCTT		
FRMD7-mutation (c.57+1G>A)-f	CCTCGCTGAGAATGCTAC	189	[a]
FRMD7-mutation (c.57+1G>A)-r	ATCACAGTCCTCCTTCAT		

[a]Touch down PCR program. PCR, polymerase chain reaction; FRMD7, FERM domain containing 7.

domains. The conserved domains are at the B41 and FERM-C domains. The B41 domain is located between residues 1-192, and the FERM-C domain is located between residues 186-279.

Many mutations in FRMD7 have been reported in Chinese families with CMN. In the current study, the authors attempted to identify FRMD7 mutations and investigate the clinical phenotype of sporadic cases with CMN in the Chinese population. In the present study, there were seven FRMD7 gene mutations, six of which 6 gene mutations are newly-identified in 7 patients with CMN. The screening

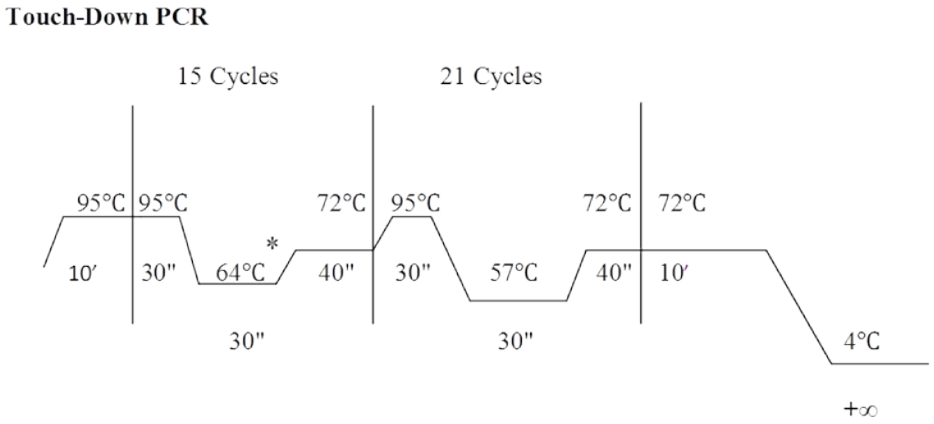

Figure 1. The touch down PCR program. *Temperature drop of 0.5°C per cycle. PCR, polymerase chain reaction.

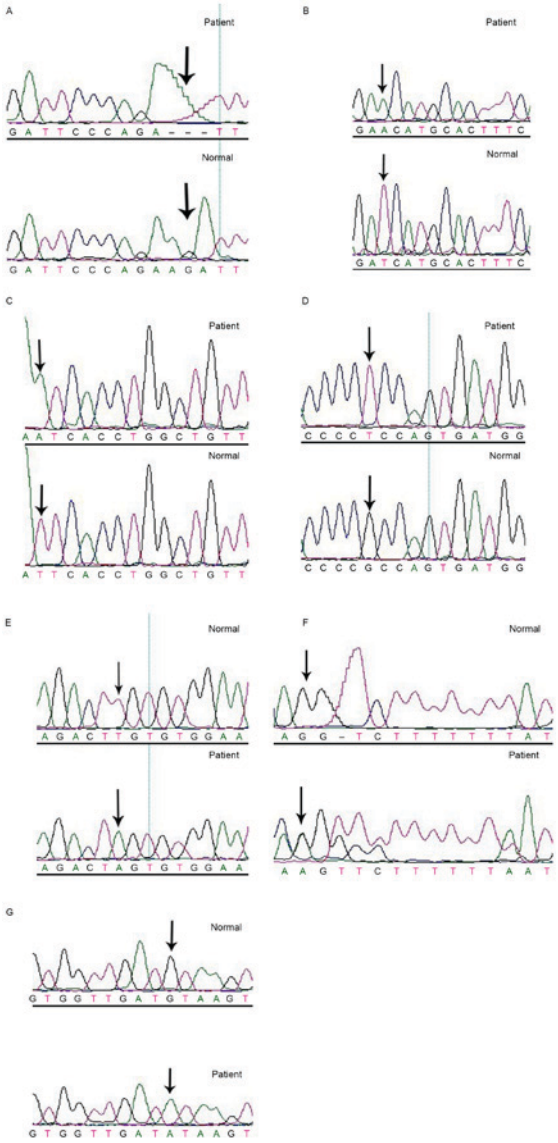

Figure 2. The map of FRMD7 direct sequencing. The mutations of (A) c.41_43delAG, (B) c.473T>A (p.I158N), (C) c.605T>A (p.I202N), (D) c.580G>T (p.A194S), (E) c.811T>A (p.C271S), (F) c.1492-1493insA (p.Y498X) and (G) c.57+1G>A were identified in the patient with congenital motor nystagmus and confirmed by bidirectional sequencing, which the arrow indicates. The other arrow shows the corresponding normal sequence from the unaffected control individual.

rate is was 38.89%, which is consistent with the previous studies (17,18).

Through the MegAlign program, the protein sequences of different species were compared and mutation sites were identified (p.I158N, p.I202N, p.A194S and p.C271S), possessing relative conservation. Though further analysis of missense mutations, it was demonstrated that mutations of p.I158N, p.I202N and p.C271S mutations are possibly damaging with scores ranging from 0.997 to 0.998. The mutation of p.A194S is was benign, but with a score of 0.993.

FRMD7 is highly expressed in regions of the developing brain that are involved in oculomotor control, as well as in the retina (16). FRMD7 may serve a role in development of the oculomotor neural circuitry, previous studies indicate that nystagmus-associated mutations in the FERM and FA domains are likely to be critical to FRMD7 function (19). The mutations of c.41_43delAGA (p.13-15delK), c.473T>A (p.I158N), c.605T>A (p.I202N), c.580G>T (p.A194S) and c.811T>A (p.C271S) are in the conserved region of FRMD. Of them, the mutations of c.41_43delAGA (p.13-15delK), c.473T>A (p.I158N), c.580G>T (p.A194S) are in the B41 domain. The mutations of c.605T>A (p.I202N) and c.811T>A (p.C271S) are in the FERM-C domain. CMN-associated missense mutations within the N-terminal region of the protein indicate that mutations can disrupt the interaction with other proteins, preventing their co-localization at the plasma membrane and impairing neurite formation (20).

The mutation site of p.Y498X is in the FERM-adjacent (FA) domain. FA is identified in a subset of FERM domain proteins, and which has been indicated to regulate protein function through modifications such as phosphorylation (21).

In summary, CMN is a genetically heterogeneous ocular movement disease. The presented result expands the mutation spectrum of FRMD7 and provides evidence for future functional studies, clinical diagnosis, differential diagnosis and genetic counseling. In conclusion, these results enriched the gene mutation spectrum of FRMD7. The authors systematically investigated the clinical phenotype of congenital motor nystagmus in the Chinese population, and provided further evidence for clinical diagnosis and differential diagnosis and genetic counseling.

Table II. Analysis by Blosum62 and PolyPhen.

Gene	Mutation	Blosum62	PolyPhen	Score
FRMD7	I158N	4→-3	Possibly damaging	0.998
FRMD7	I202N	4→-3	Possibly damaging	0.998
FRMD7	A194S	4→1	Benign	0.993
FRMD7	C271S	9→-1	Possibly damaging	0.997

FRMD7, FERM domain containing 7.

Table III. The visual acuity of patients with CMN.

Patient	Age (years)	Uncorrected visual acuity	Corrected vision
QT276	18	$0.3^{+}/0.5^{-}$	NA
QT321	12	0.2/0.1	0.4/0.4
QT370	0.3	Perception of light	ND
QT385	28	$0.7^{+}/0.8$	$0.7^{+}/0.8$
QT423	8	0.1/0.1	0.3/0.3
QT439	12	1.0/0.7	1.0/0.7
QT474	10	$0.5/0.4^{+}$	0.7/0.8
QT552	3.5	0.25/0.2	ND
QT596	5	0.3/0.3	0.4/0.4
QT664	3	0.4/0.4	0.5/0.5
QT669	3.5	ND	ND
QT684	5	0.3/0.4	$0.7/0.7^{+}$
QT712	3	Perception of light	ND
QT719	29	0.1/0.1	0.9/0.9
QT726	8	0.5/0.5	ND
QT756	5.5	$0.4^{+}/0.4^{+}$	0.7/0.6
QT762	6	0.3/0.3	0.4/0.4
QT835	1	Perception of light	ND

ND, not determined; NA, not applicable; CMN, congenital motor nystagmus.

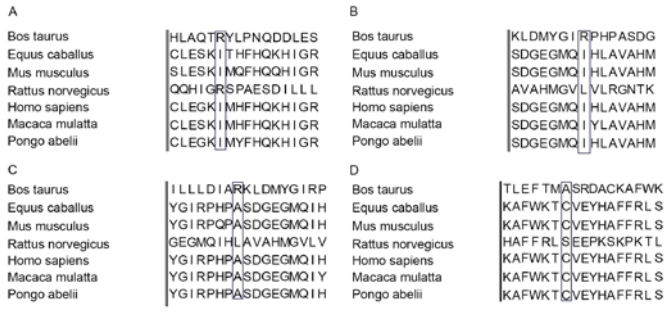

Figure 3. Analysis of conservation of mutations, which is demonstrated by analysis of seven orthologs from different mammalians. (A) As presented in the highlighted region, the mutation of p.I158N is relatively conserved in FRMD7. (B) As presented in the highlighted region, the mutation of p.I202N is relatively conserved for FRMD7. (C) As presented in the highlighted region, the mutation of p.A194S is relatively conserved in FRMD7. (D) As presented in the highlighted region, the mutation of p.C271S is relatively conserved in FRMD7.

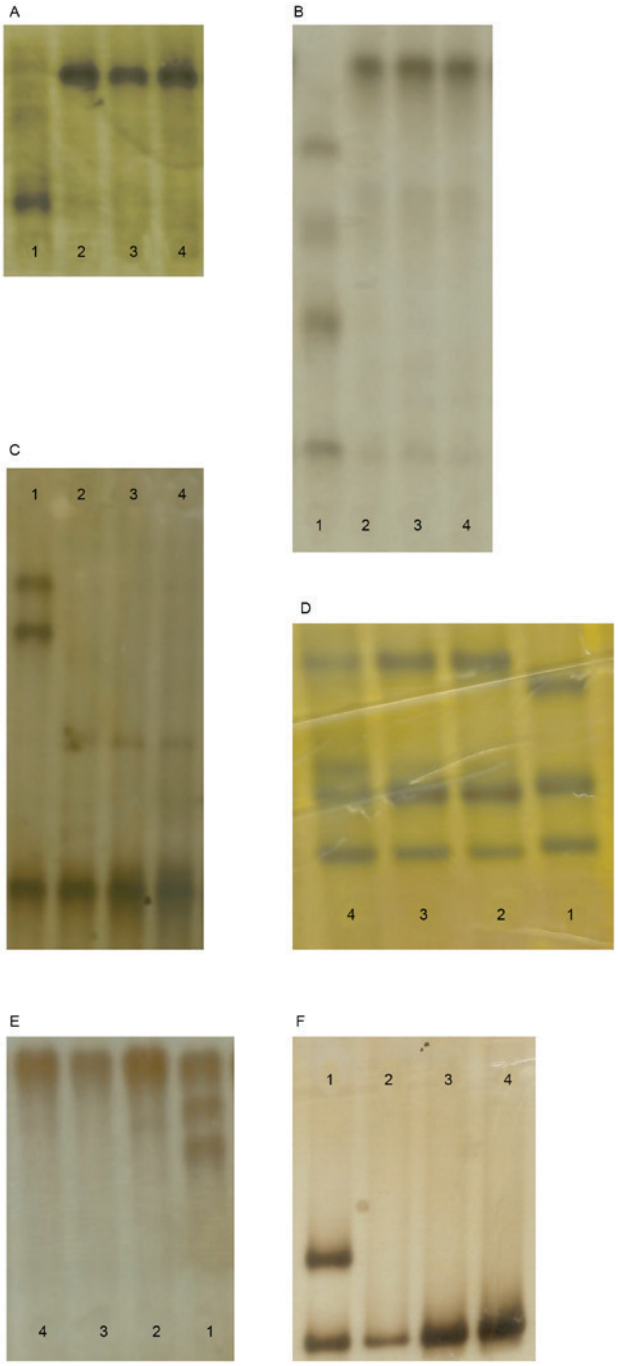

Figure 4. The HA-SSCP analysis of FRMD7 gene mutation in patients with CMN. Lane 1s indicate the bands of patients with mutation of (A) c.473T>A (p.I158N), (B) c.605T>A (p.I202N), (C) c.580G>T (p.A194S), (D) c.811T>A (p.C271S), (E) c.1492-1493insA (p.Y498X) and (F) c.57+1G>A, and the other lanes show the bands of normal controls.

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