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FRMD7-associated Infantile Nystagmus Syndrome

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Infantile nystagmus syndrome (INS) is a genetically heterogeneous disorder. To date, more than 100 genes have been reported to cause INS and there is significant overlap in phenotypic characteristics. The most common form of X-linked INS is attributed to *FRMD7* at Xq26. Recent advances in molecular genetics have facilitated the identification of pathogenic variants of *FRMD7* and the investigation for underlying mechanisms of *FRMD7*-associated INS. This review summarizes genetic and clinical features of *FRMD7*-associated INS, and introduces updates on the pathogenesis of *FRMD7* mutation.

Key words: Infantile nystagmus syndrome, *FRMD7*

REVIEW

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INTRODUCTION

Infantile nystagmus syndrome (INS), formerly called congenital nystagmus is characterized by rhythmic involuntary oscillations of the eyes that are present at birth or during infancy [1]. It can be associated with afferent visual system disorders such as ocular albinism, anterior segment dysgenesis, and foveal hypoplasia (Fig. 1). On the other hand, idiopathic INS arises independently of any other visual or neurological disorders. This has led to speculation that idiopathic INS may be caused by abnormal development of the ocular motor system itself rather than disorders of the afferent visual pathway [2,3].

The inheritance patterns of idiopathic INS are heterogeneous and have been reported as autosomal dominant, autosomal recessive, or X-linked trait [4-6]. However, the most common form of inheritance is X-linked, which can be dominant or recessive. Three loci have been identified at Xp11.4-p11.3, Xp22, and Xq26-q27, but approximately 50% of idiopathic INS families have been linked to Xq26-q27. After Tarpey et al. first identified pathogenic mutations in *FRMD7* (MIM#300628) at Xq26, over 90 different mutations have been reported in patients with idiopathic INS [7].

This review summarizes genetic and clinical features of *FRMD7*-associated INS, and introduces updates on the pathogenesis of *FRMD7* mutation.

FRMD7 (FERM Domain-Containing 7) Structure and Function

The *FRMD7* gene consists of 12 exons and encodes a 714-residue polypeptide [6]. It contains a conserved N-terminal FERM domain (amino acids 2-282) and FERM-adjacent (FA) domain (amino acids 288-336), whereas the C-terminal region has no significant homology to other proteins (Fig. 2A). The FERM domain has 3 lobed "cloverleaf" structures: F1 (lobe A), F2 (lobe B), and F3 (lobe C). These are plasma membrane-cytoskeleton coupling proteins which bind to actin

or other cytoskeleton components. The FA domain contains conserved motifs that are potential substrates for kinases, suggesting its regulatory effect in FRMD7 protein. In situ hybridization experiments in human embryonic brain showed FRMD7 expression in neuronal tissues involved in the vestibulo-ocular reflex and optokinetic reflex such as the developing

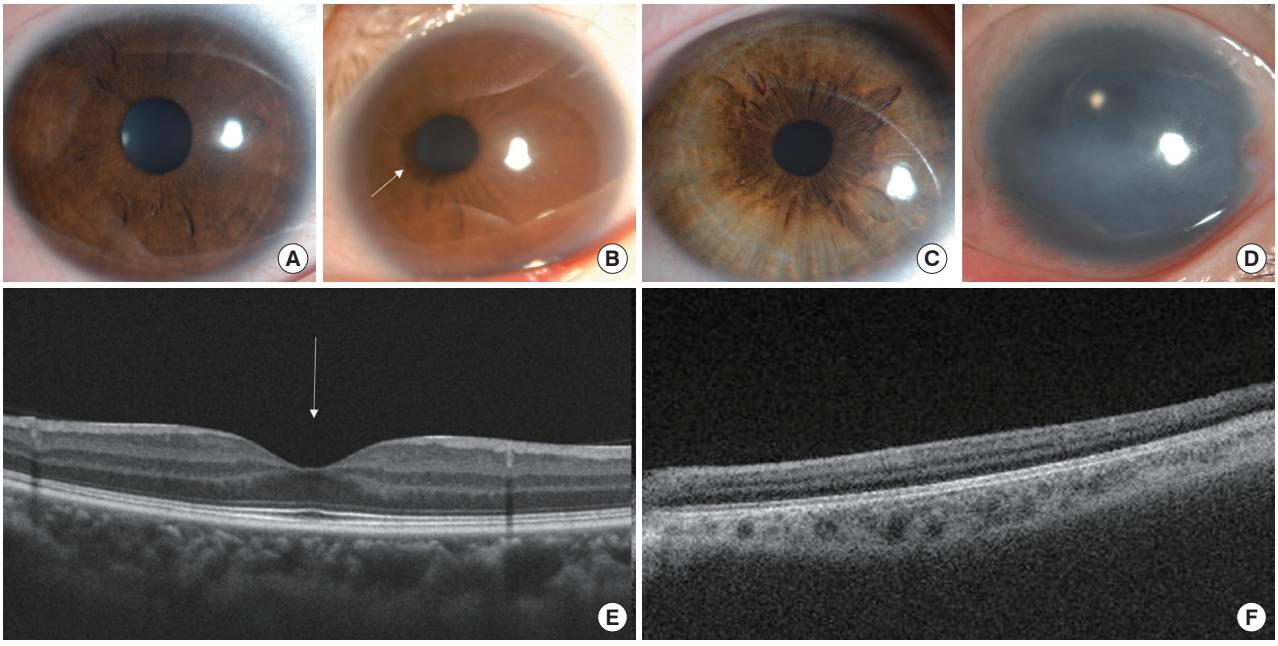

Fig. 1. Afferent visual system disorders associated with infantile nystagmus syndrome. (A) Anterior segment photography of normal eye. (B) Nasally displaced pupil with iris ectropion uvea (white arrow). (C) Iris hypopigmentation seen in ocular albinism. (D) Complete absence of the iris. (E) Optical coherence tomogram showing a normal foveal fit (white arrow). (F) Absence of foveal pit.

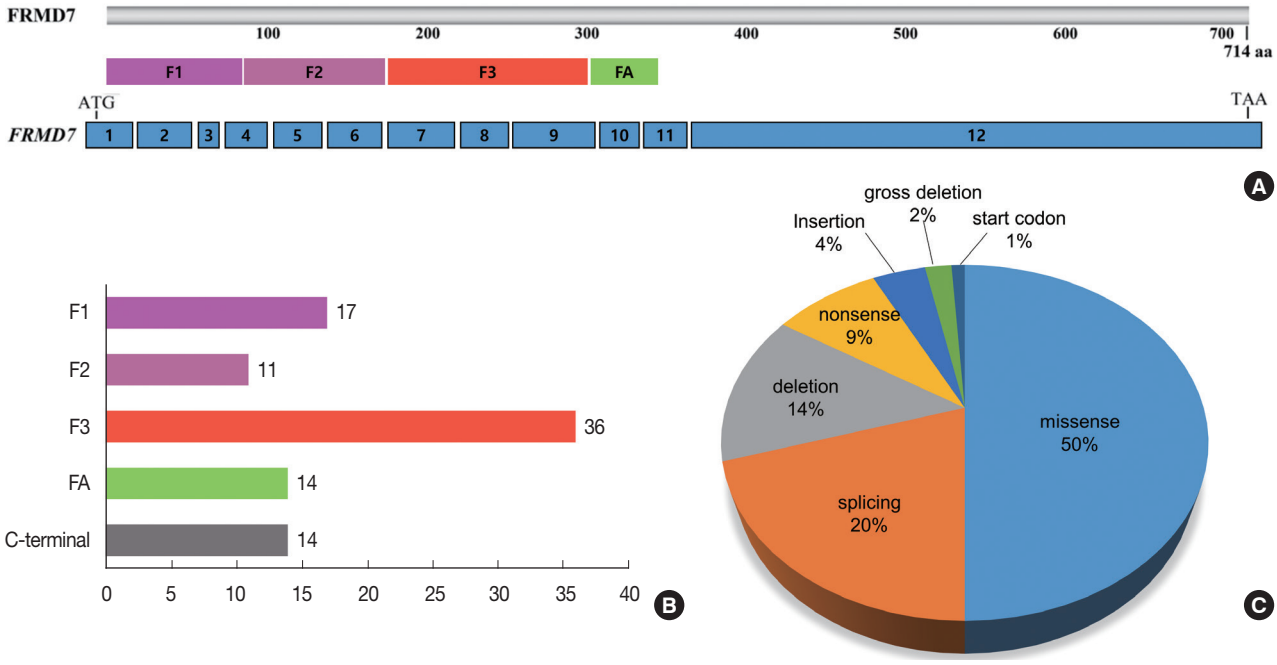

Fig. 2. (A) Schematic representation of FRMD7 protein. The FRMD7 protein contains an N-terminal FERM domain (F1, F2, and F3 lobes) and a FERM-adjacent (FA) domain. (B) Localization of *FRMD7* mutations. F3 lobe is the most mutation-rich domain. (C) Spectrum of *FRMD7* mutations. The missense mutation accounts for a half of all *FRMD7* mutations.

neural retina, optic stalk, otic vesicle, vestibulocochlear nerve, vestibular nucleus, and cerebellum [7-9].

The FRMD7 protein is highly co-localized with the actin of primary neurites in differentiating Neuro2A cells, which promotes elongation of axons and dendrites [10]. Knockdown of FRMD7 protein causes a reduction in average neurite length [11]. Several studies have proposed a mechanism of FRMD7 regulation for neuronal cytoskeletal dynamics. The FRMD7 protein shares close amino acid sequence homology with two other FERM domain containing proteins: FARP1 and FARP2 [6]. They are involved in neurite outgrowth and branching through activating Rho GTPase signaling. Rho GTPases are key regulators of the actin cytoskeleton in eukaryonic cells and mediate morphological changes during neuronal development and plasticity. It was found that wild-type human FRMD7 activated Rac1 signaling by interacting with RhoGDIα, the main regulator of Rho GTPase, while mutant FRMD7 failed to interact with RhoGDIα and to activate Rac1 signaling [12]. Recent studies also demonstrated that FRMD7 regulates the expression of Rac1 in stable SHSY-5Y cells [13], and mutant FRMD7 significantly influences the expression of Rac1, Cdc42, and RhoA during the induction period of human fibroblasts-reprogrammed neurons [14]. Thus, it is possible that FRMD7 is involved in the regulation of neuronal cytoskeletal dynamics through Rho GTPase signaling at the growth cone. Alternatively, the interaction between FRMD7 and calcium/calmodulin-dependent serine protein kinase (CASK) may promote the membrane extension during neurite outgrowth since the function of CASK is to link the plasma membrane to the actin cytoskeleton [15]. Furthermore, FRMD7 is specially localized in starburst cells of the mouse retina and the directional selective (DS) inhibitory input from starburst cells to DS ganglion cells is lost in FRMD7 mutant mice [16]. A recent study found FRMD7 to directly interact with the loop between transmembrane domains 3 and 4 of GABRA2, a type A gamma-aminobutyric acid (GABA) receptor subunit, and colocalization of FRMD7 and GABRA2 was found in the mouse retina [17]. Thus, *FRMD7* mutations perturb the interaction between FRMD7 and GABRA2, which may impair GABA inhibitory inputs from starburst cells to DS ganglion cells, eventually leading to the loss of optokinetic reflex that can be seen in INS patients. All of these findings support that nystagmus by *FRMD7* mutations may result from defective axogenesis, dendritogenesis, and neuronal guidance in the areas of the brain which control eye movements.

FRMD7 Mutations

To date, over 90 different mutations within *FRMD7* have been reported (Supplementary Table S1) [18,19]. Approximately 84% of mutations concentrates heavily within the N-terminal FERM and FA domain without any consistent hot spots (Fig. 2B). Most have been identified in single case with idiopathic INS, but some mutations including c.41delAGA (p.K14del), c.70G>A (p.G24R), c.875T>C (p.L292P), c.910C>T (p.R303X), and c.1003C>T (p.R335X) have been detected in different racial groups. Especially, c.875T>C (p.L292P) accounted for more than 50% of Korean patients carrying *FRMD7* mutations [19]. All patients with c.875T>C came from the same restricted region (Gyeongsangnam-do) of Korea, and shared two single-nucleotide polymorphisms (rs6637934, rs5977623) of exon 12 within *FRMD7*, suggesting that c.875T>C might have arisen from the founder effect in the Korean population with idiopathic INS.

A half of the mutations are missense which may destabilize the overall structure of FRMD7 protein, while the other half are predicted to cause gross defects at the protein level due to nonsense mutations, frameshift by small deletion or insertion, aberrant splicing, and large intragenic deletion (Fig. 2C). Among the 12 exons, exon 9 represents the most common mutation-rich exon (23%), followed by exon 12 (12%) and exon 8 (11%).

Incomplete penetrance was observed in female carriers, ranged from 30 to 100% [5,20-23]. This phenomenon has been explained by skewed X-inactivation and interactions with disease-modifying genes or environmental factors. Although skewed X-inactivation has consistently been suggested as a mechanism that may influence the penetrance of X-linked disorders in females, some studies have revealed that there was no clear causal link between X-inactivation pattern and phenotype in INS families with *FRMD7* mutation [20,21]. Furthermore, affected females showed random X-inactivation, reflecting a tissue mosaicism [22]. Different methylation patterns for the X chromosome were also found between female carriers, implying that a molecular basis for variable methylation might not be involved in the dissimilar penetrance [21]. Further investigations of X-inactivation status of *FRMD7* may help understand the incomplete pattern of inheritance.

Clinical Features of *FRMD7*-associated INS

The clinical features of *FRMD7*-associated INS are not much different from those of non-*FRMD7* INS. The nystagmus is present at birth or during infancy, and usually manifests as

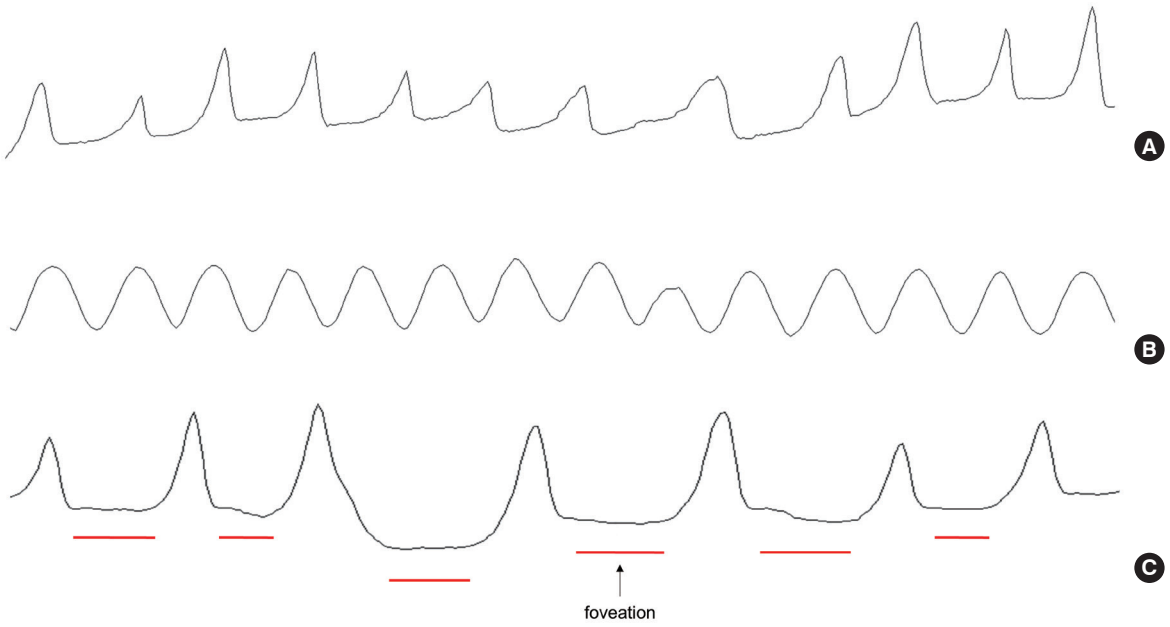

Fig. 3. Nystagmus waveforms recorded by video-nystagmography. (A) Jerk nystagmus with slow phases that drift away from the fixation position with increasing velocity waveforms. (B) Pendular nystagmus showing sinusoidal oscillations. (C) Foveation period (red bars) which the eye velocity is at or near zero.

horizontal conjugate oscillations, while vertical nystagmus is not typical for *FRMD7*-associated INS [1,4]. The direction of the nystagmus changes with eccentric gaze (right-beating on right gaze and left-beating on left gaze) or alternates periodically with time (periodic alternating nystagmus) [8,19]. The nystagmus is often accentuated by anxiety, attention, and attempts to fixate an object, while attenuated with eyelid closure or on convergence. The nystagmus waveform can be pendular or jerk with increasing exponential slow phases (Fig. 3A and 3B), but a pendular waveform is more common in adults with *FRMD7* mutations.

The nystagmus decreases when the eyes are moved into a particular position within the orbit, called the null point or zone [1]. Some individuals with INS tend to turn their head close to the null point or zone, resulting in abnormal head posture (AHP). The presence of AHP often leads parents to bring a child for medical evaluation and treatment.

Despite continuous eye oscillations, individuals with *FRMD7*-associated INS show relatively good visual acuity and no oscillopsia due to the presence of foveation period which the eye velocity is at or near zero (Fig. 3C). During this brief period, the image of the target is relatively stationary in the foveal area, leading to good visual acuity without oscillopsia [1]. Furthermore, *FRMD7*-associated INS is not accompanied with afferent visual system disorders causing reduced visual acuity such as foveal anomaly or retina dystrophy. Although previous studies have revealed morphological changes of retina and optic nerve such as decreased peripapillary retinal nerve fiber layer and shallow foveal pit and optic nerve head, these changes may be subclinical [9,18,19]. However, some individuals may complain of oscillopsia when the nystagmus is pronounced or the individual is tired.

CONCLUSION

FRMD7 is a major disease-causing gene of idiopathic INS. Although the molecular pathogenesis of *FRMD7* is still unclear, it is thought that *FRMD7* may participate in neuronal development in the areas of the brain controlling ocular motor and gaze stability. Further functional investigation and mutant analysis are needed to reveal the pathogenic mechanisms of *FRMD7*-associated INS.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

The authors have no financial conflicts of interest.

REFERENCES

1. Leigh RJ, Zee DS. The Neurology of Eye Movements, 5th edn. Oxford University Press, New York; 2015.
2. Brodsky MC, Dell'Osso LF. A unifying neurologic mechanism for infantile nystagmus. JAMA Ophthalmol 2014;132(6):761-8.
3. Richards MD, Wong A. Infantile nystagmus syndrome: clinical characteristics, current theories of pathogenesis, diagnosis, and management. Can J Ophthalmol 2015;50(6):400-8.
4. Gottlob I, Proudlock FA. Aetiology of infantile nystagmus. Curr Opin Neurol 2014;27(1):83-91.
5. Self J, Lotery A. A review of the molecular genetics of congenital Idiopathic Nystagmus (CIN). Ophthalmic Genet 2007;28(4): 187-91.
6. Watkins RJ, Thomas MG, Talbot CJ, Gottlob I, Shackleton S. The Role of FRMD7 in Idiopathic Infantile Nystagmus. J Ophthalmol 2012;2012:460956.
7. Tarpey P, Thomas S, Sarvananthan N, Mallya U, Lisgo S, Talbot CJ, et al. Mutations in FRMD7, a newly identified member of the FERM family, cause X-linked idiopathic congenital nystagmus Nat Genet 2006;38(11):1242-4.
8. Thomas MG, Crosier M, Lindsay S, Kumar A, Thomas S, Araki M, et al. The clinical and molecular genetic features of idiopathic infantile periodic alternating nystagmus. Brain 2011;134(Pt 3): 892-902.
9. Thomas MG, Crosier M, Lindsay S, Kumar A, Araki M, Leroy BP, et al. Abnormal retinal development associated with FRMD7 mutations. Hum Mol Genet 2014;23(15):4086-93.
10. Betts-Henderson J, Bartesaghi S, Crosier M, Lindsay S, Chen HL, Salomoni P, et al. The nystagmus-associated FRMD7 gene regulates neuronal outgrowth and development. Hum Mol Genet 2010;19(2):342-51.
11. Pu J, Lu X, Zhao G, Yan Y, Tian J, Zhang B. FERM domain containing protein 7 (FRMD7) upregulates the expression of neuronal cytoskeletal proteins and promotes neurite outgrowth in Neuro-2a cells. Mol Vis 2012;18:1428-35.
12. Pu J, Mao Y, Lei X, Yan Y, Lu X, Tian J, et al. FERM domain containing protein 7 interacts with the Rho GDP dissociation inhibitor and specifically activates Rac1 signaling. PLoS One 2013;8 (8):e73108.
13. Pu J, Mao Y, Xu L, Zheng T, Zhang B. Stable cell lines of human SH-SY5Y uniformly expressing wild-type or mutant-type FERM domain containing 7 gene. Exp Ther Med 2017;14(3):2277-83.
14. Pu J, Dai S, Gao T, Hu J, Fang Y, Zheng R, et al. Nystagmus-related FRMD7 gene influences the maturation and complexities of neuronal processes in human neurons. Brain Behav 2019;9(12): e01473.
15. Watkins RJ, Patil R, Goult BT, Thomas MG, Gottlob I, Shackleton S. A novel interaction between FRMD7 and CASK: evidence for a causal role in idiopathic infantile nystagmus. Hum Mol Genet 2013;22(10):2105-18.
16. Yonehara K, Fiscella M, Drinnenberg A, Esposti F, Trenholm S, Krol J, et al. Congenital Nystagmus Gene FRMD7 Is Necessary for Establishing a Neuronal Circuit Asymmetry for Direction Selectivity. Neuron 201;89(1):177-93.
17. Jiang L, Li Y, Yang K, Wang Y, Wang J, Cui X, et al. FRMD7 Mutations Disrupt the Interaction with GABRA2 and May Result in Infantile Nystagmus Syndrome. Invest Ophthalmol Vis Sci 2020; 61(5):41.
18. Choi JH, Shin JH, Seo JH, Jung JH, Choi KD. A start codon mutation of the FRMD7 gene in two Korean families with idiopathic infantile nystagmus. Sci Rep 2015;5:13003.
19. Choi JH, Jung JH, Oh EH, Shin JH, Kim HS, Seo JH, et al. Genotype and phenotype spectrum of FRMD7-associated infantile nystagmus syndrome. Invest Ophthalmol Vis Sci 2018;59(7): 3181-8.
20. Self JE, Shawkat F, Malpas CT, Thomas NS, Harris CM, Hodgkins PR, et al. Allelic variation of the FRMD7 gene in congenital idiopathic nystagmus. Arch Ophthalmol 2007;125(9):1255-63.
21. He X, Gu F, Wang Y, Yan J, Zhang M, Huang S, et al. A novel mutation in FRMD7 causing X-linked idiopathic congenital nystagmus in a large family. Mol Vis 2008;14:56-60.
22. Kaplan Y, Vargel I, Kansu T, Akin B, Rohmann E, Kamaci S, et al. Skewed X inactivation in an X linked nystagmus family resulted from a novel, p.R229G, missense mutation in the FRMD7 gene. Br J Ophthalmol 2008;92(1):135-41.
23. Wu S, Deng S, Song Z, Xu H, Yang Z, Liu X, et al. A Disease-Causing FRMD7 Variant in a Chinese Family with Infantile Nystagmus. J Mol Neurosci 2019;67(3):418-23.

Supplementary Table S1. A list of the FRMD7 mutations reported in the literature

Domain	Exon	Nucleotide	Protein	Class	Origin	Reference
	1	c.1A>G	p.M1V	Start codon	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
F1	1	c.41delAGA	p.K14del	Deletion	England, China	Tarpey P. Nat Genet 2006; Zhang Q. Mol Vis 2007; Bai D. Sci China Life Sci 2017; Jia X. Mol Med Rep 2017
	1	c.47T>C	p.F16S	Missense	Russia, England, China	Gudzenko S. Genomic Med 2008; Thomas MG. Brain 2011; Wu S. J Mol Neurosci 2019
	1i	c.57+1G>A		Splicing	China	Jia X. Mol Med Rep 2017
	1i	c.57+5G>A		Splicing	Germany	Schorderet DF. Hum Mutat 2007
	1i	c.58-1G>A		Splicing	England	Thomas MG. Brain 2011
	2	c.58C>T	p.Q20*	Nonsense	Germany	Schorderet DF. Hum Mutat 2007
	2	c.70G>A	p.G24R	Missense	Ireland, China, England, Belgium, France	Tarpey P. Nat Genet 2006; Zhang Q.Mol Vis 2007; Thomas MG. Brain 2011; AlMoallem B, Invest Ophthalmol Vis Sci 2015; Michaud V. Ophthalmic Genet 2019
	2	c.70G>T	p.G24W	Missense	China	Li N. Mol Vis 2008
	2	c.71G>A	p.G24E	Missense	Austria	Tarpey P. Nat Genet 2006
	2i	c.162+2T>C		Splicing	China	Bai D. Sci China Life Sci 2017
	2i	c.162+5G>A		Splicing	England	Tarpey P. Nat Genet 2006
	2i	c.162+6T>C		Splicing	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
	2i	c.163-1G>T		Splicing	China	Hu Y. Mol Vis 2012
	3i	c.205+2T>G		Splicing	England	Tarpey P. Nat Genet 2006
	3i	c.206-1G>A		Splicing	China	Bai D. Sci China Life Sci 2017
	3i	c.206-5T>A		Splicing	England	Thomas MG. Hum Mol Genet 2014
F2	4	c.252G>A	p.V84=	Splicing	England	Tarpey P. Nat Genet 2006
	4	c.284G>T	p.R95M	Missense	China	Bai D. Sci China Life Sci 2017
	4i	c.284+1G>A		Splicing	England	Tarpey P. Nat Genet 2006; Self JE. Arch Ophthalmol 2007
	4i	c.285-118C>T		Splicing	England	Thomas MG. Hum Mol Genet. 2014
	6	c.425T>G	p.L142R	Missense	Ireland, America	Tarpey P. Nat Genet 2006; Shiels A. Mol Vis 2007
	6	c.436C>T	p.R146W	Missense	China	Zhang Q. Mol Vis 2007
	6	c.473T>A	p.I158N	Missense	China	Jia X. Mol Med Rep 2017
	6	c.479insT	p.H160Lfs*13	Insertion	England	Tarpey P. Nat Genet 2006
	6i	c.497+5G>A		Splicing	Belgium	AlMoallem B. Invest Ophthalmol Vis Sci 2015
	6i	c.498-2A>G		Splicing	America	Schorderet DF. Hum Mutat 2007
	6i	c.498-3C>T		Splicing	China	Yan N. BMC Med Genet 2019
F3	7	c.521A>T	p.D174V	Missense	China	Bai D. Sci China Life Sci 2017
	7	c.556A>G	p.M186V	Missense	India	Gupta S. Neurosci Lett 2015
	7	c.575A>C	p.H192P	Missense	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
	7	c.580G>A	p.A194T	Missense	China	Jiang L. Invest Ophthalmol Vis Sci 2020
	7	c.580G>T	p.A194S	Missense	China	Jia X. Mol Med Rep 2017
	7	c.586G>A	p.D196N	Missense	China	Bai D. Sci China Life Sci 2017
	7	c.601C>T	p.Q201*	Nonsense	Italy-Germany	Tarpey P. Nat Genet 2006
	7	c.605T>A	p.I202N	Missense	China	Jia X. Mol Med Rep 2017
	7	c.623A>G	p.H208R	Missense	China	Li N. Mol Vis 2011
	7i	c.645+1G>C		Splicing	Madagascar	Tarpey P. Nat Genet 2006
	8	c.657G>T	p.K219N	Missense	Russia	Gudzenko S. Genomic Med 2008
	8	c.660del	p.N221Ifs*11	Deletion	Belgium	AlMoallem B. Invest Ophthalmol Vis Sci 2015
	8	c.A661G	p.N221D	Missense	England	Tarpey P. Nat Genet 2006
	8	c.673T>G	p.W225G	Missense	Switzerland	Schorderet DF. Hum Mutat 2007
	8	c.676G>A	p.A226T	Missense	England	Tarpey P. Nat Genet 2006
	8	c.685C>T	p.R229C	Missense	China	Zhang Q. Mol Vis 2007; Bai D. Sci China Life Sci 2017
	8	c.685C>G	p.R229G	Missense	Turkey	Kaplan Y. Br J Ophthalmol 2008
	8	c.691T>G	p.L231V	Missense	Ireland-Germany	Tarpey P. Nat Genet 2006; Thomas MG. Brain 2011
	8	c.694_695delAG	p.S232Ffs*2	Deletion	China	Li N Mol Vis 2008

(*Continued to the next page*)

Supplementary Table S1. Continued

Domain	Exon	Nucleotide	Protein	Class	Origin	Reference
	8	c.719T>C	p.I240T	Missense	China	Zhu Y. Sci Rep 2013
	8	c.722A>G	p.K241R	Missense	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
	9	c.766T>A	p.F256I	Missense	China	Bai D. Sci China Life Sci 2017
	9	c.780C>A	p.S260R	Missense	China	Zhang X. Sci Rep 2014
	9	c.781C>G	p.R261G	Missense	China	Zhang B. Mol Vis 2007;Zhao H. BMJ Open 2016
	9	c.782G>A	p.R261Q	Missense	China	Li N. Mol Vis 2008; Bai D. Sci China Life Sci 2017
	9	c.G796C	p.A266P	Missense	England	Tarpey P. Nat Genet 2006
	9	c.801C>A	p.F267L	Missense	Belgium	AlMoallem B. Invest Ophthalmol Vis Sci 2015
	9	c.804G>T	p.W268C	Missense	Russia	Gudzenko S. Genomic Med 2008
	9	c.805A>C	p.K269Q	Missense	China	Wang Z. Acta Biochim Biophys Sin 2019
	9	c.811T>C	p.C270R	Missense	China	Bai D. Sci China Life Sci 2017
	9	c.811T>A	p.C271S	Missense	England	Thomas MG. Brain 2011; Jia X. Mol Med Rep 2017
	9	c.812G>A	p.C271Y	Missense	Scotland	Tarpey P. Nat Genet 2006; Thomas MG. Brain 2011
	9	c.812G>T	p.C271F	Missense	China	He X. Mol Vis 2008; Li N. Mol Vis 2008
	9	c.814G>T	p.V272L	Missense	China	Li ND. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2008
	9	c.823_829delACCCTAC	p.T275fs	Deletion	China	Chen J. BMC Med Genet 2019
	9	c.824A>C	p.H275P	Missense	America	Schorderet DF. Hum Mutat 2007
FA	9	c.875T>C	p.L292P	Missense	Belgium, Korea, Japan	AlMoallem B. Invest Ophthalmol Vis Sci 2015; Choi JH. Invest Ophthalmol Vis Sci 2018; Kohmoto T. Hum Genome Var 2015
	9	c.880dupA	p.S294Kfs*9	Insertion	England	Self JE. Arch Ophthalmol 2007
	9	c.886G>C	p.G296R	Missense	China, Belgium	Zhang B. Mol Vis 2007; AlMoallem B, Invest Ophthalmol Vis Sci 2015
	9	c.886G>T	p.G296C	Missense	China	Xiu Y. Mol Med Rep 2018
		c.887delG	p.G296Vfs*23	Deletion	Austria	Tarpey P. Nat Genet 2006
	9	c.901T>C	p.T301H	Missense	Korea	Rim JH. JAMA Ophthalmol 2017
	9	c.902A>G	p.Y301C	Missense	England, Russia	Tarpey P. Nat Genet 2006; Gudzenko S. Genomic Med 2008
	10	c.910C>T	p.R303X	Nonsense	China, Belgium, Korea	Li N. Mol Vis 2008; AlMoallem B, Invest Ophthalmol Vis Sci 2015; Rim JH. JAMA Ophthalmol 2017
	10	c.917A>G	p.Q305R	Missense	India	Radhakrishna U. Eur J Hum Genet 2012
	10	c.973A>G	p.R325G	Missense	China	Bai D. Sci China Life Sci 2017; Jiang L. Invest Ophthalmol Vis Sci 2020
	11	c.980_983delATTA	p.P329E	Deletion	China	Song FW. J Zhejiang Univ Sci B 2013
	11	c.998dupA	p.H333Qfs*2	Insertion	China	Jiang L. Invest Ophthalmol Vis Sci 2020
	11	c.999delT	p.H333fs	Deletion	China	Bai D. Sci China Life Sci 2017
	11	c.1003C>T	p.R335*	Nonsense	England, India, Chinese	Tarpey P. Nat Genet 2006; Guo Y. Can J Ophthalmol 2014
C-terminal	11	c.1019C>T	p.S340L	Missense	Romania	Tarpey P. Nat Genet 2006
	11i	c.1050+1G>C		Splicing	Germany	Tarpey P. Nat Genet 2006
	11i	c.1050+5G>A		Splicing	Saudi Arabia	Khan AO. Arch Ophthalmol 2011
	12	c.1090C>T	p.Q364*	Nonsense	China	Zhao H. BMJ Open 2016
	12	c.1262delC	p.P421Lfs*23	Deletion	England	Tarpey P. Nat Genet 2006
	12	c.1275_1276delTG	p.E426Afs*4	Deletion	China	He X. Genet Test 2008
	12	c.1419_1422dup	p.T475fs	Insertion	China	Wang F. J Clin Lab Anal 2020
	12	c.1458C>T	p.Q487*	Nonsense	China	Zhang X. Sci Rep 2014
	12	c.1486_1489delTTTT	p.F497fs2*	Deletion	China	Du W. Mol Vis 2011
	12	c.1492delT	p.Y498Mfs*26	Deletion	Russia	Gudzenko S. Genomic Med 2008
	12	c.1493insA	p.Y498*	Nonsense	China	Jia X. Mol Med Rep 2017
	12	c.1524G>A	p.W508*	Nonsense	Russia	Gudzenko S. Genomic Med 2008
	12	c.1645delG	p.V549Yfs*554	Deletion	China	Zhang X.Sci Rep 2014
	12	c.2036del	p.L679Rfs*8	Deletion	Belgium	AlMoallem B. Invest Ophthalmol Vis Sci 2015
F1-F2	2_4	c.58-?_c.284+?		Large deletion	America	Fingert JH. Ophthalmic Genet 2010
All	2-12	c.(235+1_236-1)_(*3202_?)del		Large deletion	England	Thomas MG. Eur J Hum Genet 2017