

CASE REPORT

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# X-linked inheritances recessive of congenital nystagmus and autosomal dominant inheritances of congenital cataracts coexist in a Chinese family: a case report and literature review

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## Abstract

**Background:** Congenital nystagmus (CN) and congenital cataracts are distinct eye diseases and are usually isolated. Cases with CN and congenital cataracts caused by different genes in one family have been rarely reported.

**Case presentation:** A 27-year-old man presented with CN and congenital cataracts and he underwent cataract extraction 2 weeks after birth. Three years later, he had posterior chamber intraocular lens implantation. The proband's mother was only afflicted by bilateral lens opacities. Lensectomy was performed in both eyes at age 15. The proband's daughter had bilateral central cataracts and no nystagmus. She had undergone cataract extraction when she was two months old. In this family, 8 affected individuals were affected by bilateral cataracts, and three of them presented with CN. The genetic analysis was performed using a specific Hereditary Ophthalmological Disease Gene Panel on proband and his parents (one of which was a patient). PCR and Sanger sequencing verified the presence of these variants in all members of the family. The novel mutation, c.498-3C > T, in *FRMD7* explains why X-Linked recessive inheritance of CN was found in a subset of patients. A heterozygous mutation of the *GJA8* gene (c.139G > C), was identified in all patients and thus explains the autosomal dominant pattern of inheritance of congenital cataracts within the family.

**Conclusions:** This is the first time that *FRMD7* and *GJA8* gene mutations have been linked to the pathogenesis of a family with both CN and congenital cataracts. The phenomenon of two different genetic patterns coexisting in one family is rare.

**Keywords:** Case report, Congenital nystagmus, Congenital cataracts, *FRMD7*, *GJA8*, Chinese pedigree

## Background

Congenital nystagmus (CN) are ocular motor disorders in which patients are afflicted by periodic involuntary ocular oscillations affecting both eyes [1, 2]. Disease onset normally occurs at birth or develops shortly thereafter. The inheritance model of CN has been previously described in various forms as being either autosomal or X-linked, and either dominant or recessive, with X-linked

inheritance and incomplete penetrance being the most common [3]. Three distinct X-linked loci are known: Xp11.4-p11.3, Xq26-Xq27, and Xp22.3-p22.2 [4–6]. The Xq26-q27 and Xp22.3-p22.2 regions contain genes coding for FERM domain-containing 7 (*FRMD7*) and G-protein coupled receptor 143 (*GPR143*), respectively, and both of these genes have been identified as contributors to CN disease [6, 7]. The *GPR143* gene is also associated with X-linked ocular albinism type 1 (OA1) [8, 9].

Congenital cataracts are by far the most common explanation for blindness in children globally, with such blindness being characterized by lens opacity [10]. It is

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estimated that blindness occurs in approximately 1–6 of every 10,000 births in highly developed countries, and at higher rates of 5–15 per 10,000 births in those countries which are poorer [11–13]. As many as one in three congenital cataracts are believed to be linked to specific genetic mutations [14, 15]. Over 48 genes have been identified in the inherited forms of isolated or primary cataracts with minimal other ocular signs [15]. Most often, inherited cataracts not associated with another known disease present a pattern of autosomal dominant (AD) inheritance, but this is not always the case and in some instances X-linked or autosomal recessive (AR) versions are evident [16].

In our study, four generations of a family from China afflicted CN and congenital cataracts were recruited. Some of the affected individuals exhibited CN, and all were afflicted by congenital cataracts. Patients were sequenced to find candidate genes within the family. We identified two different genetic patterns that coexist in the family. Mutations in *FRMD7* and *GJA8* genes were responsible for the pathogenesis of CN and congenital cataracts respectively.

### Case presentation

The proband (patient III: 1, Fig. 1a, Fig. 1b, Fig. 2a) is a 27-year-old who previously underwent cataract extraction 2 weeks after birth. Three years later, he had posterior chamber intraocular lens implantation but he did not receive any amblyopia treatment, nor did he use aphakic spectacle for visual rehabilitation following the two surgeries. He was found to have nystagmus on the fortieth day after birth and was diagnosed with CN. His daughter (IV: 1) had bilateral central cataracts and no nystagmus. She had undergone cataract extraction when she was two months old. Visual rehabilitation via aphakic spectacle correction using +20 diopter sphere (DS) in the right eye and +21DS in the left eye was performed.

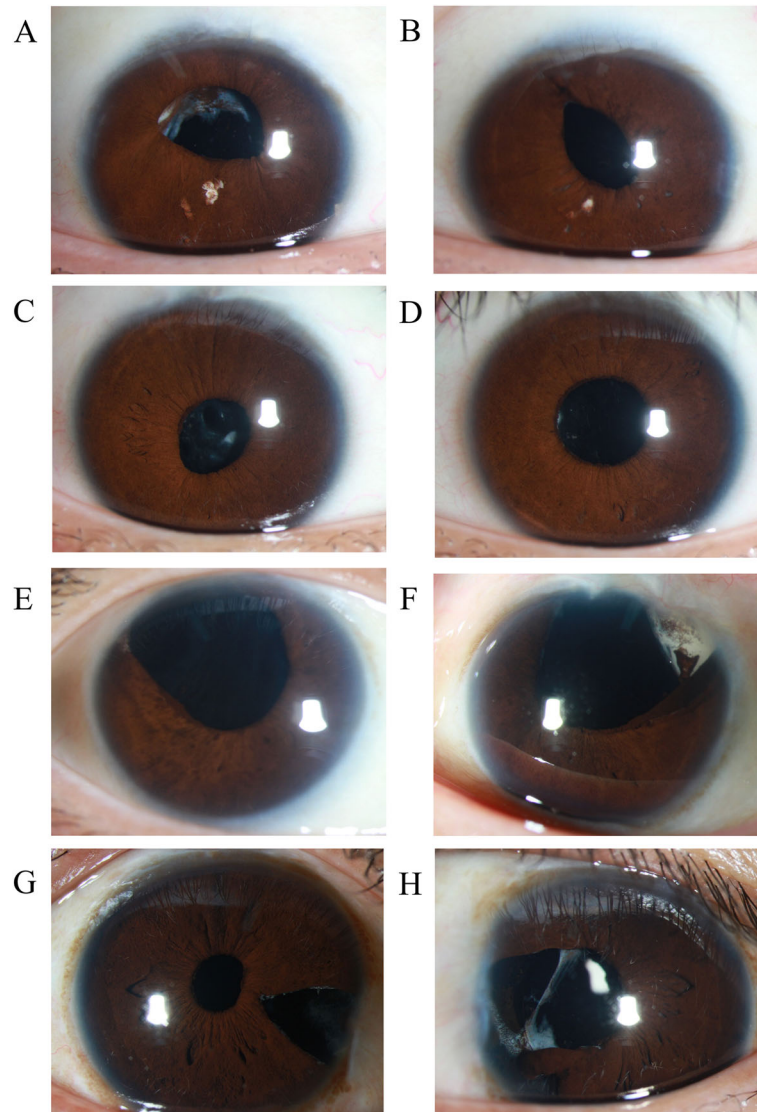
The proband's brother (III: 3, Fig. 1c, Fig. 1d) had bilateral cataracts and conjugate horizontal nystagmus. He underwent cataracts extracted at age 6 and had an intraocular lens implanted at age 11. The proband's mother (II:1, Fig. 1e, Fig. 1f) was additionally afflicted by bilateral lens opacities. Lensectomy was performed in both eyes at age 15. The proband's uncle (II:3, Fig. 1g, Fig. 1h) also had bilateral congenital cataracts without nystagmus. He had phacoemulsification cataract extraction and intraocular lens implantation when he was 28 years old. His two daughters (III: 4, III: 5) were found to have bilateral central cataracts without nystagmus. They both had phacoemulsification cataract extractions and intraocular lens implantations when they were 9 years old. The patient features are described in Table 1 and this family was recruited from West China Hospital, Sichuan University. All participants were informed about the purpose of the

protocol and signed consent forms. The protocol was approved by the Ethics Committee of West China Hospital, Sichuan University.

Patient III:1, his mother (II:1, patient) and his father (II:1, normal) were sequenced by with a specific Hereditary Ophthalmological Disease Gene Panel. DNA was extracted using QIAamp DNA blood mini kit (Qiagen) and exons coinciding with genes of interest being captured via the Panel with biotinylated oligo-probes (GenCap Enrichment Technologies, MyGenostics, Beijing). A total of 662 genes, including most known to related to hereditary ophthalmological disease, were included in this panel (see Additional file 1: Table S1). An Illumina Solexa HiSeq 2000 sequencer (MyGenostics, Beijing) was used for sample sequencing. Bioinformatics analysis was performed to identify the mutations were linked to the disease phenotype present in the affected family. Sanger sequencing was verified the variants in other individuals using primers: *FRMD7* (NG\_012347) forward primer CATCTGGCACAAACTCGGTA and reverse primer CTCTTAAAACCTCAACTTGC GGA. *GJA8* (NG\_016242) forward primer GAACATCTTGGAGGAGGTGAAT and reverse primer CAGAGGCGAATGTGGGAGAT.

More than 99% of the targeted regions were covered in each sample. Using bioinformatics analysis, two candidate mutations were identified in this family. A heterozygous mutation in *GJA8* gene (chr1–14,738,022, exon2, c.139G > C, p.D47H, NM\_005267.4) and a novel *FRMD7* gene splicing mutation (chrX-131,219,759, exon7, c.498-3C > T, splicing, NM\_194277.2) were found in patient III:1 (Other variants results of Patient III:1 to see Additional file 2: Table S2). The c.139G > C mutation of *GJA8* gene was found in ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/variation/280147/>) (Clinical significance: Pathogenic) and not found in gnomAD database. The c.498-3C > T mutation of *FRMD7* gene was not found in ClinVar database and gnomAD database. Segregation analysis was performed in the other family members using Sanger sequencing. The *GJA8* heterozygous mutation c.139G > C was found in all patients and is likely responsible for autosomal dominant inheritance of congenital cataracts (Fig. 2a, Fig. 2c). The *FRMD7* splicing variant c.498-3C > T was found in I:1, III:1 and III:3. II:1 and IV:1 were carriers (Fig. 2b, Fig. 2d). This segregation pattern is consistent with X-Linked recessive inheritance. These two mutations had paternal origin and came down from I:1, and the mutations were absent in those family members unaffected by disease. The sequence results of all the patients and some normal family members were shown in the Additional file 3: Figure S1 and Additional file 4: Figure S2.

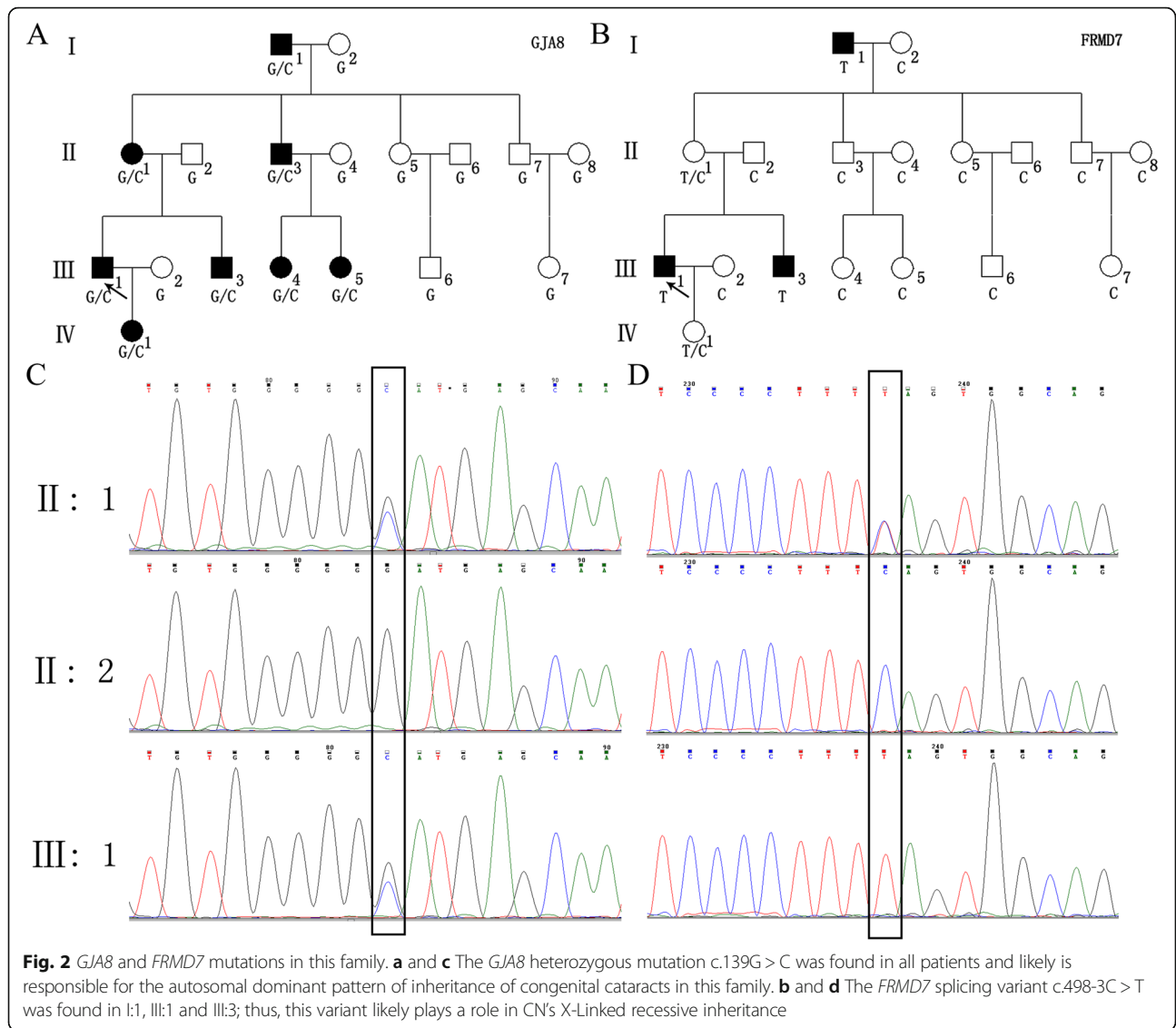
A computational analysis of the D47H *GJA8* mutant using a Polymorphism Phenotyping (PolyPhen-2) analysis yielded a result predicting this mutation to be



**Fig. 1** Slit-lamp photograph of patients who had congenital cataracts. **a:** Right eye of the proband III:1. The pupil is upward. Thickened capsule can be seen. Intraocular lens is located in the right position. **b:** Left eye of the proband III:1. The pupil is not round. Intraocular lens is located in the right position. **c:** Right eye of patient III: 3. Pupil is not perfectly round. **d:** Left eye of patient III:3. Pupil is round. Intraocular lens is located in the right position. **e:** Right eye of patient II:1. Irregularly shaped pupil can be seen. Aphakia. **f:** Left eye of patient II:1. The iris has anterior adhesion from the 3 o'clock to 5 o'clock position. **g:** Right eye of patient II:3. There is a hole of circumferential iridectomy. Intraocular lens is located in the right position. **h:** Left eye of patient II:3. The pupil deformation is severe with capsule thickened

“probably damaging”, while Sorting Intolerant From Tolerant (SIFT) analysis similarly suggested an intolerant substitution. Human *FRMD7* is 2145 bp in length, with a total of 12 exons. A novel splice variant c.498-3C>T of *FRMD7* had been found comparing with the original form of *FRMD7*. A novel isoform of *FRMD7* arises through the alternative splicing of *FRMD7* mRNA, leading to the deletion of 148 bp in exon 4. Through the “Deep Learning” algorithm of SPIDEX, the *dpsi\_max\_tissue* score was  $-0.1228$ , and the *dpsi\_z* score was  $-0.514$ . The score range is  $-100$  to  $100$ . The closer the

absolute value of the score is to  $100$ , the greater the influence of mRNA splicing. The *dbscSNV* analysis found that the *ada\_score* was  $0.6943564$  (the score range is  $0-1$ , the greater the score is, the greater the impact; the normal value is no more than  $0.6$ ), and the *rf\_score* was  $0.232$  (the score range is  $0-1$ ; the greater the score is, the greater the impact; the normal value is no more than  $0.6$ ). If one of these scores is greater than  $0.6$ , *dbscSNV* is T (TRUE), and otherwise, it is F (FALSE) (Table 2). According to the ACMG guidelines, the c.139G>C variation of *GJA8* gene was “pathogenic” and the



**Table 1** Summary of clinical features of patients

ID	Gender	Age (years)	Congenital nystagmus	Congenital cataracts	Cataract surgery	BCVA (OD/OS)
I: 1	Male	74	Yes	Yes	No	HM/HM
II: 1	Female	48	No	Yes	15 years old	HM/HM
II: 3	Male	45	No	Yes	28 years old	0.2/0.06
III: 1	Male	27	Yes	Yes	cataract extraction 2 weeks after birth, lens implantation at 3 years old	0.02/0.2
III: 3	Male	24	Yes	Yes	cataract extraction at 6 years old, lens implantation at 11 years old	0.02/0.1
III: 4	Female	20	No	Yes	9 years old	0.1/0.08
III: 5	Female	21	No	Yes	9 years old	0.2/0.1
IV: 1	Female	1	No	Yes	cataract extraction two months after birth	—/—



c.498-3C>T variation of *FRMD7* gene was “likely pathogenic”.

## Discussion and conclusions

A Chinese family affected both by CN and by congenital cataracts was reported in our study. The phenomenon of two different types of eye diseases with different genetic patterns of inheritance in a family is very rare. No similar results have been reported.

The D47H *GJA8* mutation has previously been linked to congenital nuclear and zonular pulverulent cataracts, and has the same cataract type as this family [17]. The *GJA8* coding region consists of one exon and encodes 432 amino acids. Over 24 distinct *GJA8* mutations have been reported to date in humans and in mouse models, with direct evidence that these mutations promote the formation of cataracts [18]. The c.139G>C substitution leads to the substitution of a histidine in place of aspartic acid at position 47, leading to a change from negative to positive charge [17]. Aspartic acid at position 47 is found in the extracellular loop E1 region of *GJA8* [19]. Consistent with Li's study, our PolyPhen and SIFT results suggest that D47H is a likely loss-of-function mutation [17].

It has been reported that the knockout of *GJA8* in mice results in cataract development the impairment of lens growth [20]. *GJA8* is highly expressed in both epithelial and lens fiber cells, particularly during their differentiation [21]. The mutated *GJA8* alters lens fiber cell formation, which in turn leads to cataract formation [20].

*FRMD7* mutations are major causes of CN [7]. *FRMD7* expression is primarily detectable within the retina and vestibular system, with additional expression in portions of the brain regulating the vestibulo-ocular reflex [7, 22]. It has been reported that *FRMD7* is important to facilitate neuronal circuit asymmetry for directional selectivity [23]. Nevertheless, exactly what role is played by *FRMD7* is still uncertain. The protein encoded by *FRMD7* has an N-terminal FERM domain that may facilitate signal transduction, similar to other proteins in this family with this same domain [23].

**Table 2** In Silico Prediction of c.139G>C of *GJA8* and c.498-3C>T of *FRMD7*

PolyPhen	score	meaning
	1.000	probably damaging
SIFT	score	meaning
	0.02	intolerant
SPIDEX:	dpsi_max_tissue	dpsi_zscore
	-0.1228	-0.514
dbSNV:T(TRUE)	ada_score	rf_score
	0.6943564	0.232

Interestingly, most mutations leading to congenital nystagmus are located in this FERM domain [22].

A *FRMD7* splice variant (*FRMD7-S*) has previously been cloned and identified. This variant form may be important in the context of neuronal differentiation and development [24]. Another splice variant, *FRMD7* (*FRMD7\_SV2*), is similarly predicted to be important for neuron development [25]. The *FRMD7* mutation of c.206-5 T>A is predicted to disrupt the splice acceptor site in the third intron, while variant c.205 + 2 T>G is predicted to be pathological on the basis of its likelihood to induce nonsense-mediated decay or exon skipping [26]. In this family, a novel splice variant of *FRMD7*, c.498-3C>T, has been identified. This splice variant was predicted to be harmful using bioinformatics analysis and this variant is likely the causative lesion for CN in this family.

In summary, this study reveals two variants of two genes. These variants explain two clinical pathologies with different inheritance patterns in a Chinese family. The exact means by which these variants result in CN and congenital cataracts at the molecular level remains to be determined, and further functional studies will be necessary to offer novel insights into this inherited ocular disease.

## Additional files

**Additional file 1: Table S1.** The panel of genes screened for the family (662) (XLSX 17 kb)

**Additional file 2: Table S2.** Other variants results of Patient III:1. (XLSX 14 kb)

**Additional file 3: Figure S1.** Sanger sequence of *GJA8* gene. The sequence results of *GJA8* c.139G>C mutation in all the patients and some normal family members. (TIF 3118 kb)

**Additional file 4: Figure S2.** Sanger sequence of *FRMD7* gene. The sequence results of *FRMD7* c.498-3C>T splicing variant in all the patients and some normal family members. (TIF 2876 kb)

## Abbreviations

AD: autosomal dominant; AR: autosomal recessive; CN: Congenital nystagmus; DS: diopter sphere; *FRMD7*: FERM domain-containing 7; GPR143: G-protein coupled receptor 143; OA1: ocular albinism type 1; PolyPhen-2: Polymorphism Phenotyping; SIFT: Sorting Intolerant From Tolerant

## Acknowledgments

We thank the patient in this case study and his family for participating in the study. We would like to thank MyGenostics (Beijing) for providing computational analysis.

## Funding

This work was supported by the National Natural Science Foundation of China (NSFC) (grant no. 81500697), including study design, data analysis and writing the manuscript.

## Availability of data and materials

The relevant data were generated during this study and included in this article (see supplementary information files). And raw sequence data were not applicable to share in this article as no datasets were generated during the current study.

**Authors' contributions**

NY, LX and KM carried out the experiments, prepared the figures, and drafted the manuscript. CH and B.G. performed bioinformatics analysis of sequencing data. WF and YD conceived the study, participated in its design and coordination. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of West China Hospital, Sichuan University. All participants were informed about the purpose of the protocol and signed consent forms. The guardian (parent) of the patients (under the age of 16) consented to participation of the study.

**Consent for publication**

Written informed consent was obtained from the patient for publication of this Case Report. The guardian (parent) of the patients (under the age of 18) consented to publication of the study. The guardian (parent) of the patients consented for their medical information to be published.

**Competing interests**

The authors declare that they have no competing interests.

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Received: 30 October 2018 Accepted: 7 March 2019

Published online: 19 March 2019

**References**

- Casteels I, Harris CM, Shawkat F, Taylor D. Nystagmus in infancy. *Br J Ophthalmol*. 1992;76(7):434–7.
- Abadi RV, Bjerre A. Motor and sensory characteristics of infantile nystagmus. *Br J Ophthalmol*. 2002;86(10):1152–60.
- Oetting WS, Armstrong CM, Holleschau AM, DeWan AT, Summers GC. Evidence for genetic heterogeneity in families with congenital motor nystagmus (CN). *Ophthalmic Genet*. 2000;21(4):227–33.
- Cabot A, Rozet JM, Gerber S, Perrault I, Ducrocq D, Smahi A, et al. A gene for X-linked idiopathic congenital nystagmus (NYS1) maps to chromosome Xp11.4-p11.3. *Am J Hum Genet*. 1999;64(4):1141–6.
- Kerrison JB, Vagefi MR, Barmada MM, Maumenee IH. Congenital motor nystagmus linked to Xq26-q27. *Am J Hum Genet*. 1999;64(2):600–7. <https://doi.org/10.1086/302244>.
- Liu JY, Ren X, Yang X, Guo T, Yao Q, Li L, et al. Identification of a novel GPR143 mutation in a large Chinese family with congenital nystagmus as the most prominent and consistent manifestation. *J Hum Genet*. 2007;52(6):565–70. <https://doi.org/10.1007/s10038-007-0152-3>.
- 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. <https://doi.org/10.1038/ng1893>.
- Bassi MT, Schiaffino MV, Renieri A, De Nigris F, Galli L, Bruttini M, et al. Cloning of the gene for ocular albinism type 1 from the distal short arm of the X chromosome. *Nat Genet*. 1995;10(1):13–9. <https://doi.org/10.1038/ng0595-13>.
- Mackey DA. 2005 Gregg lecture: congenital cataract—from rubella to genetics. *Clin Exp Ophthalmol*. 2006;34(3):199–207. <https://doi.org/10.1111/j.1442-9071.2006.01194.x>.
- Shiels A, Hejtmancik JF. Genetic origins of cataract. *Arch Ophthalmol*. 2007;125(2):165–73. <https://doi.org/10.1001/archophth.125.2.165>.
- Holmes JM, Leske DA, Burke JP, Hodge DO. Birth prevalence of visually significant infantile cataract in a defined U.S. population. *Ophthalmic Epidemiol*. 2003;10(2):67–74.
- Vogt G, Puhoe E, Czeizel AE. Population-based case-control study of isolated congenital cataract. *Birth Defects Res A Clin Mol Teratol*. 2005;73(12):997–1005. <https://doi.org/10.1002/bdra.20188>.
- Apple DJ, Ram J, Foster A, Peng Q. Elimination of cataract blindness: a global perspective entering the new millennium. *Surv Ophthalmol*. 2000;45(Suppl 1):S1–196.
- Hejtmancik JF, Smaoui N. Molecular genetics of cataract. *Dev Ophthalmol*. 2003;37:67–82.
- Shiels A, Hejtmancik JF. Molecular genetics of cataract. *Prog Mol Biol Transl Sci*. 2015;134:203–18. <https://doi.org/10.1016/bs.pmbts.2015.05.004>.
- Pichi F, Lembo A, Serafino M, Nucci P. Genetics of congenital cataract. *Dev Ophthalmol*. 2016;57:1–14. <https://doi.org/10.1159/000442495>.
- Li J, Wang Q, Fu Q, Zhu Y, Zhai Y, Yu Y, et al. A novel connexin 50 gene (gap junction protein, alpha 8) mutation associated with congenital nuclear and zonular pulverulent cataract. *Mol Vis*. 2013;19:767–74.
- Wang L, Luo Y, Wen W, Zhang S, Lu Y. Another evidence for a D47N mutation in GJA8 associated with autosomal dominant congenital cataract. *Mol Vis*. 2011;17:2380–5.
- Maeda S, Nakagawa S, Suga M, Yamashita E, Oshima A, Fujiyoshi Y, et al. Structure of the connexin 26 gap junction channel at 3.5 Å resolution. *Nature*. 2009;458(7238):597–602. <https://doi.org/10.1038/nature07869>.
- White TW. Unique and redundant connexin contributions to lens development. *Science*. 2002;295(5553):319–20. <https://doi.org/10.1126/science.1067582>.
- Gu S, Yu XS, Yin X, Jiang JX. Stimulation of lens cell differentiation by gap junction protein connexin 45. *Investigative ophthalmology & visual science*. 2003;44(5):2103–11.
- 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. <https://doi.org/10.1093/brain/awq373>.
- 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*. 2016;89(1):177–93. <https://doi.org/10.1016/j.neuron.2015.11.032>.
- Li Y, Pu J, Liu Z, Xu S, Jin F, Zhu L, et al. Identification of a novel FRMD7 splice variant and functional analysis of two FRMD7 transcripts during human NT2 cell differentiation. *Mol Vis*. 2011;17:2986–96.
- Li Y, Pu J, Zhang B. Expression of a novel splice variant of FRMD7 in developing human fetal brains that is upregulated upon the differentiation of NT2 cells. *Experimental and therapeutic medicine*. 2014;8(4):1131–6. <https://doi.org/10.3892/etm.2014.1916>.
- 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. <https://doi.org/10.1093/hmg/ddu122>.

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