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...
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 +2 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 cataract extraction 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 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 (Gen-Cap 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 performed in the other individuals using primers: FRMD7 (NG_012347) forward primer CATCTGGCACAAAACTCGGTA and reverse primer CTCCTAAAACCTCAACTTGGCGA. GJA8 (NG_016242) forward primer GAACATCTTGGAGGAGTA and reverse primer CAGAGGCAGATGGTGGGGAGAT.

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
“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 dpsis_max _tissue score was −0.1228, and the dpsis_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

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.
Fig. 2  GJA8 and FRMD7 mutations in this family.  

a and c The GJA8 heterozygous mutation c.139G > C was found in all patients and likely is responsible for the autosomal dominant pattern of inheritance of congenital cataracts in this family. 

b and d The FRMD7 splicing variant c.498-3C > T was found in I:1, III:1 and III:3; thus, this variant likely plays a role in CN’s X-Linked recessive inheritance.

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 introduction 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, impairing lens fiber cell formation, which in turn leads to cataract formation [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 for facilitating 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].

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 under 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 exact means by which these variants result in CN 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.

### Table 2

| PolyPhen   | score | meaning              |
|------------|-------|----------------------|
| SIFT       |       |                      |
|            | 1.000 | probably damaging    |
|            | 0.02  | intolerant           |
| SPIDEX     |       |                      |
|            | −0.1228|                      |
|            | −0.514|                      |
| dbscSNV/T  |       |                      |
|            | ada_score| rf_score            |
|            | 0.6943564| 0.232              |

**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

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**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.
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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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