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CASE REPORT Open Access

Detection of an *FYCO1* nonsense mutation in an affected patient with autosomal recessive cataract (CTRCT18): a case report

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Abstract

Background: Autosomal recessive cataract (CTRCT18) is a rare type of congenital cataract that develops to complete and lifelong childhood blindness. This inherited disorder is one of the major visual health concerns in infants. Genetic studies discovered that various gene mutations resulted in congenital cataracts. This study reports an 8-month-old affected boy from a consanguineous family with a diagnosis of congenital cataract and a causative genetic abnormality.

Case presentation: In this study, we applied whole-exome sequencing (WES) followed by Sanger sequencing to identify probable gene defects in an affected patient with a congenital cataract. We found a homozygous disease-causing *FYCO1* gene mutation (c.1387 G > T; p.G463X), located in exon 8 (NM_024513), causing a nonsense mutation that has been resulted in the stop codon. Parents are heterozygous for the detected mutation.

Conclusions: Our findings establish that this detected *FYCO1* gene mutation is a pathogenic variant causing autosomal recessive cataract.

Keywords: Autosomal recessive cataract, *FYCO1*, Whole-exome sequencing, Case report

Background

Cataracts, caused by a decrease in the degree of clarity of the lens of the eye, are characterized by symptoms such as blurred vision, extreme sensitivity to light, diplopia, poor night vision, or blurred vision. There are different types of cataracts. The first type can be due to aging. Over time, the lens hardens and loses its sharpness. Other conditions include illness such as diabetes or corticosteroids due to trauma to the eye, family history, prolonged exposure to sunlight, history of surgery or inflammatory bowel disease, and alcohol consumption and smoking noted. Congenital cataract (CC) is an initial event of impaired vision and complete blindness that should be monitored in the first days of birth or during 1 year of old [1]. CC triggers from alterations in lens structure that lead to an ocular lens opacification or clouding of the eye lens [2].

It has been reported that congenital cataract is a major visual health challenging issue with a mean prevalence rate of 7.5 per 10,000 children worldwide [3]. Moreover, it accounts for more than half of infants and childhood blindness cases [3]. Although disease percentage varies in different countries worldwide, studies showed that Asia with a high prevalence rate is a hotbed of disease [4].

Autosomal recessive (AR) cataract (CTRCT18) is a rare type of congenital cataract that develops to complete and lifelong childhood blindness [5] and as an inherited disorder is one of the major visual health concerns in infants [6, 7].

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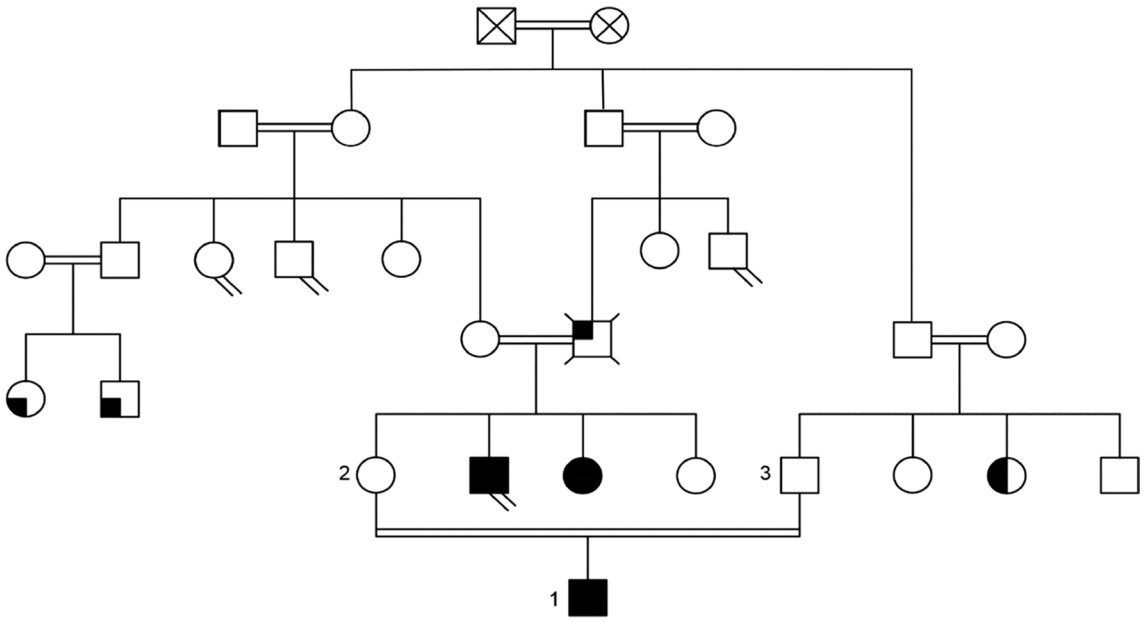

Fig. 1 Pedigree of the studied family. Patient 1 was an 8-month-old affected boy in the presented study. The parents of the affected son (2, 3) are first cousins

Although it has been reported that CC is a multifactorial abnormality, genetic investigations elucidated that this heterogeneous disorder is associated with a wide causative and underlying gene defects, including mutations in more than 100 genes that are related to the disease manifestations [3, 8]. AR cataract-associated genes so far were consisted of *FYCO1, BFSP2, GCNT2, AGK, AKR1E2, RNLS, DNMBP, EPHA2, GJA8, CRYAB, MIP, GJA3*, etc. [9], and it is demonstrated that most of the known related genes involved in the differentiation and progression of lens placode as well as autophagy procedure [10].

Therefore, whole-exome sequencing (WES) can be applied as a useful diagnostic method to identify disease-causing mutations in affected patients [3]. We reported a case of AR cataract with a disease-causing mutation in the coiled-coil domain containing 1 (*FYCO1*) gene. To discover the causative genetic defect, in this case, we conducted WES and Sanger sequencing.

Table 1 Reported mutations in the *FYCO1* gene

Pathogenic variant	Protein effect	Type of mutation	Phenotype
c.1045 C > T	p.Gln349Ter	Nonsense	Congenital cataracts
c.1546 C > T	p.Gln516Ter	Nonsense	Congenital cataracts
c.2206 C > T	p.Gln736Ter	Nonsense	Congenital cataracts
c.2761 C > T	p.Arg921Ter	Nonsense	Congenital cataracts
c.2830 C > T	p.Arg944Ter	Nonsense	Congenital cataracts
c.3670 C > T	p.Arg1224Ter	Nonsense	Congenital cataracts
c.449T > C	p.Ile150Thr	Missense	Cataract, recessive pediatric
c.4127T > C	p.Leu1376Pro	Missense	Congenital cataracts
IVS9 ds + 1 G > T	–	Splicing	Congenital cataracts
IVS9 as − 2 A > C	–	Splicing	Cataract, autosomal recessive
IVS14 as − 1 G > C	–	Splicing	Congenital cataracts

Case presentation

In the present study, we genetically analyzed an Iraqi family with an 8-month-old boy who suffered from a congenital cataract (Fig. 1). The patient was the first-born and only child to healthy first cousin parents. A history of inherited cataracts was claimed in siblings of his consanguine parents.

The patient was referred to medical genetics for cataract and visual impairment. An ophthalmologist did a complete eye exam and diagnosis. Further assessment revealed unusual rapid eye movements (nystagmus) and the pupil's "red-eye" glow loss. Parents were healthy individuals with no eye complications.

Whole-exome sequencing

Once the genomic DNA was extracted from the buffy coat that was detailed in the FAVORGEN manufacturer's protocol (Biotech Corp, Cat. No.: FABGK 001, Taiwan), the DNA samples were analyzed for concentration and quality by using Thermo NanoDrop One (Thermo Fisher, USA) with a concentration of 100–200 ng/μl and 1.8–2.0 ratio in 260/280 nm.

We solely performed WES for the proband. Data analysis revealed that there is a novel single mutation (c.1387 G > T; p.G463X), located in exon 8 (NM_024513) of the *FYCO1* gene causing a nonsense mutation, predicting an alteration in codon translation, and finally change to stop codon. No mutation was detected in other genes. The MutationTaster and SIFT predicted that G463X variant is disease-causing. In addition, the search for rare variants (frequency less than 1%), which were particularly found in the affected boy, was carried out by using Exome Aggregation Consortium (ExAC) and 1000 Genomes databases. Reported mutations in the *FYCO1* gene are summarized in Table 1 based on Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php).

PCR reaction

The PCR reaction was carried out by Bio-Rad Thermocycler as following: 12.5 μL Master Mix 2X (Thermo Scientific), 1μL DNA, 0.5 μL forward primer, 0.5 μL reverse primer, and H2O up to a final volume of 25 μL. Genomic DNA was PCR-amplified using the forward primer TAC GGCATCAGACACAAAGG and the reverse primer CTGCTGCAAAGCCTGGTAAT. The PCR reaction was performed as follows: initial denaturation at 95 °C for 5 min, followed by 35 cycles of 95 °C for 60 s, 65 °C for 40 s, and 72 °C for 60 s.

Sanger sequencing

To validate the candidate mutation, we sequenced the PCR products using the automated genetic analyzer (ABI-3130 XL, USA). The result of the sequences data was visualized by UGENE software. Sanger sequencing confirmed this single-nucleotide variant (c.1387 G > T; p.G463X) in the proband and his healthy parents. The detected mutation was found in the homozygous state in the affected patient and heterozygous state in his parents (Fig. 2).

Discussion

Prevention of childhood blindness in the concept of congenital cataracts was among the main objectives in vision 2020 [11]. So, it is claimed that this growing and high prevalence pediatric disorder should be seriously managed [10]. Investigations in the area of molecular etiology in inherited cataracts demonstrated that underlying gene abnormalities of this disorder could be divided into 4 groups, including crystallin mutations, lens membrane protein mutations, mutations of lens cytoskeletal elements, and the other remaining mutations [11]. However, most of them are included in the crystallin genes group [11].

Hence, in this study, we examined the probable disease-causing mutation in an 8-month-old affected boy, referred to medical genetics for congenital cataract and visual impairment.

In addition, this family reported a history of congenital cataracts in siblings of parents. In contrast, parents were healthy individuals without a history of eye disorder. The WES and Sanger sequencing were used to identify the impaired gene in this family, and a homozygous pathologic *FYCO1* (c.1387 G > T; p.G463X) mutation associated with AR infantile cataract was detected in the patient (8-months-old boy), followed by heterozygous mutations in his consanguine parents. This substitution leads to premature termination of the *FYCO1* protein by converting the glycine at position 463 to a stop codon, can create major problem in the *FYCO1* protein.

The *FYCO1* gene, which is located on chromosome 3 (3p21.31), consists of 18 exons (NM_024513.4) and plays a crucial role in lens progression and transparency in humans [7]. In addition, it has been declared that *FYCO1* is an autophagy adaptor protein and a part of the PI(3)P-binding protein family [9]. Previous studies revealed that the AR form of CC could be a consequence of *FYCO1* gene mutations. In this regard, Chen et al., in their publication, showed causative nonsense and frameshift *FYCO1* mutations in 13 unrelated families with CC. Furthermore, Hira Iqbal et al. evaluating pathogenic genomic defects in three consanguineous families, introduced two novels and one known mutation in the *FYCO1* gene and concluded that mutations in *FYCO1* accounted for approximately 15% of total cases

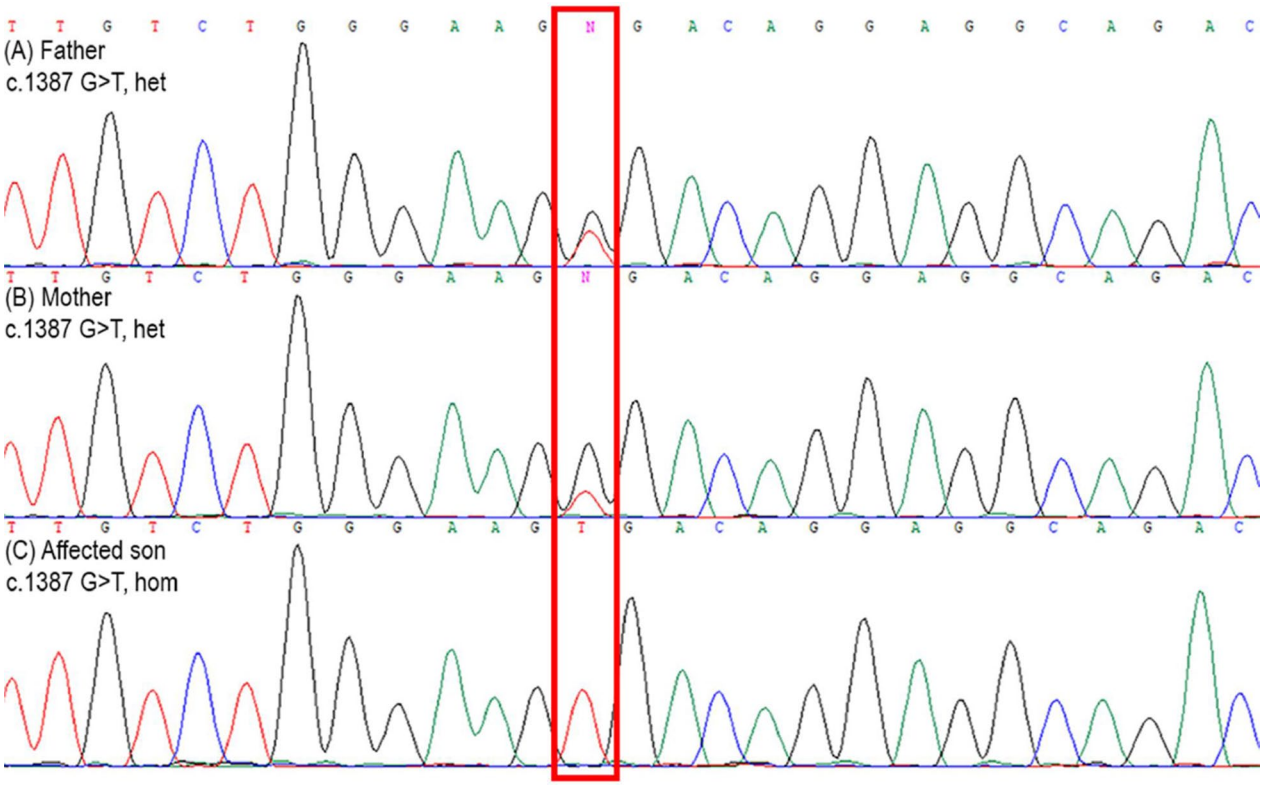

Fig. 2 Sequencing data analysis. The patient carries a homozygous nonsense mutation (c.1387 G>T; p.G463X) (**C**: affected son). Parents are heterozygous for the detected mutation (**A**, **B**)

of autosomal recessive CC [9]. Subsequently, Raffi Aprahamian et al. reported a novel homozygous pathogenic variant (c.2365 C>T) in exon 8 of the *FYCO1* gene in a Lebanese infant [12]. In line with these findings, Nikolay A. Barashkov et al. also investigated the genetic defect of CC in the Turkic-speaking Yakut population using WES and presented a novel homozygous c.1621 C>T mutation that resulted in a premature stop codon. More assessment showed that this mutation existed in 86% of CC-affected patients in this population and may be due to the founder effect [5].

Altogether, *FYCO1* gene mutations in inherited or sporadic states have been reported from various regions worldwide but in a high prevalence from Pakistan. The affected patient in our study has Iraqi descent, which in consanguineous marriage is common, so they are more susceptible to transfer abnormal genes or inherited disorders. Since identifying the genetic etiology of CC is a basic milestone of clear insights into underlying pathogenesis pathways and recognizing susceptible populations, it can help to reduce affected cases by prenatal molecular diagnosis, especially in consanguine parents or even genetic consulting before marriage [11].

Finally, it seems that this point of detected mutation is a rare mutational hotspot point that carried in patient ancestors. The obtained results and family history suggest considering this gene mutation in the genetic test platform of AR cataract cases.

Conclusion

The present study detected a case of AR cataract (CTRCT18) with a homozygote nonsense mutation (c.1387 G>T; p.G463X) in the *FYCO1* gene in an 8-month-old boy in an Iraqi family from heterozygote and carrier parents. Moreover, we show that this method can be useful for detecting rare causative genetic variants in patients with CTRCT18.

Abbreviations

AR: Autosomal recessive; CC: Congenital cataract; FYCO1: Coiled-coil domain containing 1; PCR: Polymerase chain reaction; WES: Whole-exome sequencing.

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Authors' contributions

RAA made design of the study and wrote the manuscript. RAA, AIA, MN and JMA analyzed and interpreted the data. MN edited the manuscript. HM

helped to review the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the parents of the patient. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or compare ethical strand.

Consent for publication
Written informed consent was obtained from the family for this publication.

Competing interests
The authors declared there is no conflict of interest.

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