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 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
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           |

**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.
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 Thermo-cycler 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 CTGCTGCAAGGCTTGTGTAAT. 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 gene 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.
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

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**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).
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 comparable ethical standards.

**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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