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Case Report

Case report of a CRYGS gene mutation in a patient with congenital cataracts and secondary glaucoma

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Abstract: Congenital cataracts are a major cause of visual impairment in infants and young children, with glaucoma being a frequent complication after cataract surgery. Here, we report a case of congenital cataracts accompanied by secondary glaucoma following surgery and we preliminarily investigate the genetic etiology. Comprehensive physical examination was performed, and genomic DNA extracted from the patient's was subjected to exome sequencing. A heterozygous variant of uncertain significance in the *CRYGS* gene (c.409T>C: p.Trp137Arg), associated with autosomal dominant polymorphic cataract, was identified. Familial segregation analysis indicated maternal inheritance, with a 50% transmission risk to future offspring.

Keywords: Congenital cataract, glaucoma, CRYGS gene, exome sequencing, genetic mutation

Introduction

Congenital cataract, a leading cause of visual impairment in infants and young children, manifests lens opacity at birth or during early infancy [1]. Its global prevalence is estimated at approximately at 4.24 cases per 100,000 live births, with the highest burden reported in Asia [2]. Notably, the incidence of congenital cataracts has risen steadily over time. Although early lensectomy remains a standard treatment, it carries a significant risk of secondary glaucoma, occurring in 6.60%-10.70% of postoperative cases [3-5]. Elucidating the risk factors for glaucoma following cataract surgery is essential for early identification of high-risk individuals and the development of evidence-based management strategies.

Genetic mutations are increasingly recognized as contributors to postoperative glaucoma. For instance, Boese et al. associated the *GJA3* p.Asp67Tyr variant with secondary glaucoma in patients with congenital cataracts [6]. Crystallins, critical lens proteins encoded by *CRYGS* gene, are implicated in cataractogenesis when mutated. Sun et al. detected a heterozygous 1619G→T missense mutation in *CRYGS* exons in congenital cataract patients [7], while Vendra et al. demonstrated that Y64 mutations destabilize the CRYGS protein, contributing to cataract formation [8].

Here, we present a case of congenital cataracts complicated by secondary glaucoma, in which a novel heterozygous *CRYGS* variant (c.409T>C: p.Trp137Arg) was identified via exome sequencing. This finding expands the mutational spectrum of this disorder. Our study focused on identifying gene mutations implicated in both congenital cataracts and secondary glaucoma to explore their utility as predictive biomarkers for postoperative outcomes.

Case presentation

Basic case details

A patient with congenital cataracts complicated by secondary glaucoma presented to Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology in 2021. The patient had previously undergone bilateral phacoemulsification with anterior vitrectomy on April 19, 2018, and was subsequently diagnosed with secondary glaucoma

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Table 1. A summary of the patient's baseline characteristics

Category	Data
Sex	Male
Age (years)	6
Family history	Maternal history of congenital cataracts
Clinical course	Photophobia persisting for >2 years; diagnosis of bilateral congenital cataracts with secondary glaucoma; bilateral phacoemulsification with anterior vitrectomy (April 19, 2018); readmission on December 10, 2021 for management of secondary glaucoma in both eyes

on December 10, 2021. Written informed consent was obtained from the patient and his legal guardian.

With the mother's consent, the patient's medical history was reviewed and documented, revealing a prior diagnosis of congenital cataract. Demographic and clinical data, including age, sex, height, weight, medical history, and family history, were recorded. Comprehensive ophthalmic examination was performed, including uncorrected and best-corrected visual acuity (UCVA/BCVA), slit-lamp biomicroscopy, anterior segment photography, intraocular pressure (IOP) measurement, and ocular B-mode ultrasonography. These assessments facilitated accurate diagnosis and differentiation from other ocular disorders. The patient data are shown in **Table 1**.

Exome sequencing

Genomic DNA was extracted from 5-10 mL of peripheral blood using the phenol-chloroform method. DNA purity was assessed with a NanoDrop system by measuring the absorbance (A) ratios at 260 nm and 280 nm (A260/A280). Only samples with an A260/A280 ratio >1.7 were subjected to further sequencing. A high-quality DNA library was constructed and subjected to hybridization-based target enrichment using the Agilent SureSelectXT kit. Exome sequencing was conducted on the Illumina high-throughput sequencing platform. For data analysis, sequence reads were aligned to the human reference genome (hg19) using the Burrows-Wheeler Aligner. Single-nucleotide variants and insertions/deletions (indels) were detected using Samtools. Subsequently, the identified variants were annotated using ANNOVAR and filtered against public databases, including the 1000 Genomes Project, OMIM, and the Human Gene Mutation Database (HGMD), to prioritize potentially pathogenic variants.

Single Nucleotide Polymorphism (SNP) analysis: Exome sequencing revealed a heterozygous missense variant of uncertain significance in *CRYGS* (c.409T>C; p.Trp137Arg), located at chromosome 3:186256613. This variant is associated with autosomal dominant polymorphic cataracts and is consistent with the inheritance pattern identified in this pedigree. Notably, this variant has not been previously reported in the literature or cataloged in ClinVar. Familial segregation analysis confirmed maternal inheritance of the variant, consistent with the documented family history of congenital cataract. Based on these findings, we recommend: (1) continued clinical monitoring of both the proband and the mother, and (2) comprehensive genetic counseling for the family due to the 50% risk of passing on to future offspring.

Copy Number Variation (CNV) analysis: CNV analysis results are shown in **Figure 1**. No clinically relevant copy number variations were identified in relation to the observed phenotype.

Relevant CRYGS gene sequences are as follows: gtagccattc ctgaatttct ttcagcactg ggaaaaccag tctatgcacc aaaaatgtct; aaaactggaa ccaagattac tttctatgaa gacaaaaatt ttcaaggccg tcgctatgac; tgtgattgcg actgtgcaga tttccacaca tacctaagtc gctgcaactc cattaaagtg; ccacagggag agtaccctga ataccagcgt tggatgggcc tcaacgaccg cctcagctcc; tgcagagctg ttcatctgcc tagtggaggc cagtataaga ttcagatctt tgagaaaggg; gattttagtg gtcagatgta tgaaaccacc gaagattgcc cttccatcat ggagcaattt; cacatgcgag agatccactc ctgtaaggtg ctggagggtg tctggatttt ctatgagcta; cccaactacc gtggcaggca gtacctcctg gacaagaagg agtaccggaa gcccatcgat; tggggtgcag cctccccagc tgtccagtct ttccgccgca ttgtggagta atgacatgaa; atcaataaaa cagttggcat gcatcccact gctgactata atgcctctcc ttaaatgctt; ctagggacca gcaatacagt gctcgccaca gtgggcagtc acacaaagct acccatctgc;

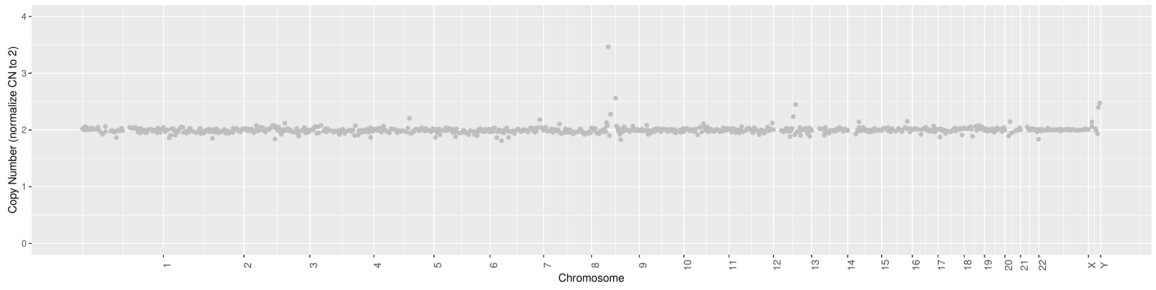

Figure 1. Copy number variation analysis results. Each dot represents the average copy number of chromosomal bands. Chromosomes are labeled along the x-axis, while the y-axis shows the relative copy number in the test sample (gray dots). Genomic regions with copy number amplifications (Gains) or deletions (Losses) are highlighted in red and green, respectively.

cagatcacca atctagatct ttgtgccaaa caaaatgaga tctcattaaa aggttagaaa; gtca.

Discussion

Congenital cataracts remain a leading cause of visual impairment in children globally, with genetic factors accounting for a substantial number of cases. Current research has identified over 30 genes associated with congenital cataract pathogenesis, among which crystallin genes represent a major subset [9]. As the principal structural proteins of the lens, crystallins are essential for maintaining its transparency and refractive properties, both of which are critical for precise image formation on the retinal [10]. The crystallin protein family comprises three evolutionarily conserved classes that exhibit distinct abundance patterns in the ocular lens: α-crystallins (~40% of total lens protein content), β-crystallins (~35%), and γ-crystallins (~25%). These proteins interact to form a highly organized and stable network that preserves lens homeostasis. Disruption of this network, whether through intramolecular conformational changes or intermolecular interactions, exposes hydrophobic regions that promote protein aggregation - a central mechanism in cataractogenesis [11]. Substantial genetic evidence supports the pathogenic role of crystallin gene mutations in congenital cataracts. For instance, a study investigating hereditary cataract pedigrees identified four novel crystallin variants segregating in four distinct families: *CRYAA* c.35G>T (p.R12L), *CRYBB2* c.463C>A (p.Q155K), *CRYGC* IVS1 c.10-1G>A, and *CRYGD* c.346delT (p.F116Sfsx29) [9]. These molecular findings highlight the necessity for systematic mutation screening and functional characterization of crystallin variants to better elucidate their precise contributions to cataract pathophysiology.

Among crystallin proteins, γ-crystallins are the simplest and smallest structural components, distinguished from other crystallins by their characteristically high cysteine residue content [12]. This unique molecular signature endows γ-crystallins with specialized biological functions. Three γ-crystallin isoforms have been identified in humans: γC, γD, and γS-crystallin [13]. Of particular interest, γS-crystallin, encoded by the *CRYGS* gene, plays a regulatory role in cataract onset and progression. Mechanistic studies have demonstrated that divalent metal ions (Cu^{2+} and Zn^{2+}) can bind to specific γS-crystallin domains, inducing subtle but pathologically significant conformational changes that promote protein aggregation and subsequent cataract formation [14]. Hence, investigating CRYGS gene variants and their functional consequences in congenital cataracts is of great importance.

Our investigation identified a novel heterozygous *CRYGS* mutation (c.409T>C, p.Trp137Arg), expanding the known mutational spectrum associated with congenital cataracts. The pathogenic role of *CRYGS* mutations in congenital cataracts is well-established. For example, Zhang et al. identified a novel missense mutation (c.199T>A, p.Tyr67Asn) in a family with autosomal dominant congenital nuclear cataracts, which was proposed to decrease local hydrophobicity and induce conformational changes in γS-crystallin, leading to its abnormal translocation from the cytoplasm to the cell membrane [13]. Similarly, Vanita et al.

reported another missense mutation of *GRYGS* (p.V42M) associated with bilateral congenital cataracts [15], while Sun et al. characterized a heterozygous mutation linked to human dominant progressive cortical cataracts [7].

The genetic mutation identified in this study demonstrates a significant association with autosomal dominant polymorphic cataracts. Accumulating evidence suggests that pathogenic *CRYGS* mutations, particularly missense or nonsense mutations, frequently induce conformation changes in γS-crystallin, thereby compromising its subcellular localization and structural stability. Based on these findings, we postulate that the heterozygous CRYGS c.409T>C (p.Trp137Arg) mutation may similarly induce affected protein conformation and function. Furthermore, familial segregation analysis confirmed maternal inheritance of the variant, indicating a 50% inheritance risk. Thus, future investigations are warranted to clarify the precise molecular mechanisms underlying this mutation and to comprehensively evaluate its potential pathogenicity and associated clinical risks.

Of note, the patient in this study developed secondary glaucoma following congenital cataract surgery, raising the possibility of an association between the *CRYGS* c.409T>C (p.Trp137Arg) mutation and an elevated risk of postoperative glaucoma. Given the well-documented correlation between postoperative glaucoma and genetic mutations, our findings suggest that this specific *CRYGS* variant may represent a potential predictive biomarker for postoperative glaucoma risk following cataract surgery. Nevertheless, further clinical evidence is needed to substantiate this hypothesis. In light of these observations, further investigation is warranted to systematically evaluate the impact of the CRYGS c.409T>C mutation on structural stability, three-dimensional conformation, and biological activity of γS-crystallin.

The current investigation has certain limitations. While our results indicate a potential association between the CRYGS c.409T>C (p.Trp137Arg) variant and congenital cataracts complicated by postoperative glaucoma, it is important to note that these findings are based on a single case. As such, the findings should be interpreted with caution until further supported by additional clinical and experimental evidence.

Conclusions

This study identified a novel pathogenic missense mutation (c.409T>C, p.Trp137Arg) in the *CRYGS* gene, potentially associated with autosomal dominant polymorphic congenital cataracts and secondary glaucoma. While this variant may serve as a candidate biomarker for predicting postoperative glaucoma risk, its clinical relevance remains uncertain and requires further validation. Familial segregation analysis indicated maternal inheritance, with a 50% transmission risk to future offspring. Therefore, future studies should aim to elucidate the pathogenic mechanisms by which the *CRYGS* c.409T>C (p.Trp137Arg) mutation contributes to congenital cataracts and glaucoma development, and to evaluate its broader clinical implications.

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Disclosure of conflict of interest

None.

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References

[1] Lenhart PD and Lambert SR. Current management of infantile cataracts. Surv Ophthalmol 2022; 67: 1476-1505.

[2] Wu X, Long E, Lin H and Liu Y. Prevalence and epidemiological characteristics of congenital cataract: a systematic review and meta-analysis. Sci Rep 2016; 6: 28564.

[3] Wang J, Chen J, Chen W, Wang Q, Zhao L, Wang R, Liu Z, Chen H, Cao Q, Tan X, Lin Z, Li X, Li J, Lai W, Zhu Y, Chen C, Zheng D, Wu M, Han Y, Chen W, Liu Y and Lin H. Incidence of and risk factors for suspected glaucoma and glaucoma after congenital and infantile cataract surgery: a longitudinal study in China. J Glaucoma 2020; 29: 46-52.

[4] Li L, Wang X, Liu C, Wang S and Wang X. Incidence rate of secondary glaucoma following congenital cataract surgery: an in-depth sys-

tematic review and meta-analysis. Am J Ophthalmol 2024; 265: 176-188.
[5] Wang J, Wu X, Wang Q, Zhou F, Chen H, Chen W, Lin D, Zhang X, Wang R, Chen J, Liu Z, Lin Z, Li X, Li J, Han Y, Liu Y, Lin H and Chen W. Incidence of and risk factors for suspected and definitive glaucoma after bilateral congenital cataract surgery: a 5-year follow-up. Br J Ophthalmol 2024; 108: 476-483.
[6] Boese EA, Drack AV, Roos BR, Alward WLM, Tollefson MR, Schnieders MJ, Scheetz TE, Boldt HC, Stone EM and Fingert JH. GJA3 genetic variation and autosomal dominant congenital cataracts and glaucoma following cataract surgery. JAMA Ophthalmol 2023; 141: 872-879.
[7] Sun H, Ma Z, Li Y, Liu B, Li Z, Ding X, Gao Y, Ma W, Tang X, Li X and Shen Y. Gamma-S crystallin gene (CRYGS) mutation causes dominant progressive cortical cataract in humans. J Med Genet 2005; 42: 706-710.
[8] Vendra VPR, Ostrowski C, Clark R, Dyba M, Tarasov SG and Hejtmancik JF. The Y46D mutation destabilizes dense packing of the second greek key pair of human gammaC-Crystallin causing congenital nuclear cataracts. Biochemistry 2023; 62: 1864-1877.
[9] Zhuang J, Cao Z, Zhu Y, Liu L, Tong Y, Chen X, Wang Y, Lu C, Ma X and Yang J. Mutation screening of crystallin genes in Chinese families with congenital cataracts. Mol Vis 2019; 25: 427-437.
[10] Roskamp KW, Paulson CN, Brubaker WD and Martin RW. Function and aggregation in structural eye lens crystallins. Acc Chem Res 2020; 53: 863-874.
[11] Wang Y, Cao K, Guo ZX and Wan XH. Effect of lens crystallins aggregation on cataract formation. Exp Eye Res 2025; 253: 110288.
[12] Serebryany E, Martin RW and Takahashi GR. The functional significance of high cysteine content in eye lens gamma-crystallins. Biomolecules 2024; 14: 594.
[13] Zhang T, Yan L, Leng Y, Chen C, Ma L, Wang Q, Zhang J and Cao L. A novel missense mutation of CRYGS underlies congenital cataract in a Chinese family. Gene 2018; 675: 9-14.
[14] Cardenas R, Fernandez-Silva A, Ramirez-Bello V and Amero C. Characterization of the interaction of human gammaS crystallin with metal ions and its effect on protein aggregation. Biomolecules 2024; 14: 1644.
[15] Vanita V, Singh JR, Singh D, Varon R and Sperling K. Novel mutation in the gamma-S crystallin gene causing autosomal dominant cataract. Mol Vis 2009; 15: 476-481.