

ORIGINAL RESEARCH ARTICLE

Genetic analysis of *GJA3* and *GJA8* mutations in cataract patients from the Jammu region, North India

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Abstract

Cataracts are a clinically and genetically heterogeneous cause of visual impairment and have multifactorial causes, in which genetic factors play a significant role. Numerous studies suggest that mutations in genes involved in maintaining lens transparency contribute to the development of cataracts. Therefore, the present study aimed to investigate the spectrum of genetic variations and mutations in the *GJA3* and *GJA8* genes in cataract patients from the Jammu region of North India. A total of 100 individuals were enrolled, consisting of 50 cataract patients (senile [$n = 35$ and congenital cataracts (CCs) [$n = 15$], diagnosed by an ophthalmologist, and 50 healthy controls. DNA was extracted, followed by amplification of the targeted regions of the *GJA8* and *GJA3* genes using polymerase chain reaction. The amplified DNA was then sequenced using the Sanger sequencing method. A novel heterozygous C>T transition at nucleotide position 759 in exon 2 of the *GJA8* gene (connexin 50) was identified in four CC patients. This silent variation caused a leucine-to-leucine substitution at amino acid position 268. Importantly, this mutation was not found in any of the 50 healthy controls or the other 46 cataract patients. No mutations were detected in the *GJA3* gene. The study concludes that this *GJA8* gene polymorphism may be a genetic risk factor for the development of CCs in the Jammu region of North India.

Keywords: Congenital cataracts; *GJA8*; *GJA3*; Genetic mutations; Jammu; North India

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1. Introduction

Cataracts, defined as any opacity in the eye lens, are the leading cause of blindness globally.¹ The disease is broadly classified into two categories: “congenital cataracts (CCs),” which are present at birth and interfere with the lens’s ability to transmit and focus light onto the retina, and “senile cataracts,” which typically develop with age and are more common in the elderly population.²⁻⁴ These cataracts can be further divided into subtypes based on their shape and location within the lens, including sutural, whole lens, nuclear, lamellar,

cortical, polar, cerulean, and coralliform cataracts.^{3,5,6} The development of cataracts has been linked to a combination of environmental and genetic factors, with genetic predisposition playing a significant role in determining susceptibility.^{7,8} Gap junction genes, such as *GJA3* and *GJA8*, which encode connexin proteins essential for cell communication and lens transparency, have emerged as key candidates for investigation (Tables S1 and S2). Notably, exon 2 in both genes has been identified as a mutation hotspot, as multiple studies have reported various mutations in this region associated with cataract formation (Tables S1 and S2).

Mutations in exon 2 are thought to disrupt the structure and function of connexins, impairing intercellular communication in the lens and leading to cataractogenesis.⁹ This study investigated exon 2 of the *GJA3* and *GJA8* genes for mutations in cataract patients from the Jammu region of North India. The findings emphasize the significance of identifying genetic causes to enable accurate diagnoses, enhance risk assessment, and improve clinical management of cataracts. Understanding the genetic basis of cataracts may also contribute to the development of targeted therapeutic approaches in the future.

2. Materials and methods

This case-control study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, and a structured overview of the study methodology is provided in Table S3.

2.1. Ethics statement

The present hospital-based case-control study was undertaken following the approval of the Institutional Ethics Committee of Government Medical College, Jammu (Letter number: IEC/GMC/2022/1091), as well as the Ethical Committee of the University of Jammu (Letter number: DRS/22/4957). Participant recruitment was carried out between June 2020 and September 2021. As the study involved patients with CCs, written informed consent was obtained from their guardians before their inclusion in the study.

2.2. Patient recruitment

This observational case-control study, conducted in 2022, enrolled 100 unrelated participants comprising 50 clinically diagnosed cataract cases (Figure 1) and 50 healthy controls in a 1:1 ratio. All participants were recruited from the Tertiary Eye Care Centre at Government Medical College Hospital, Jammu. The sample size was determined using the Sample Availability Calculator.¹⁰ All participants were recruited from a single tertiary care institution, ensuring consistency in clinical assessment and data collection. Each cataract patient underwent a thorough clinical evaluation, including detailed slit-lamp examinations, performed by Dr. Happy Kour, a specialist ophthalmologist. These evaluations allowed for accurate documentation of cataract subtypes and their associated clinical features.

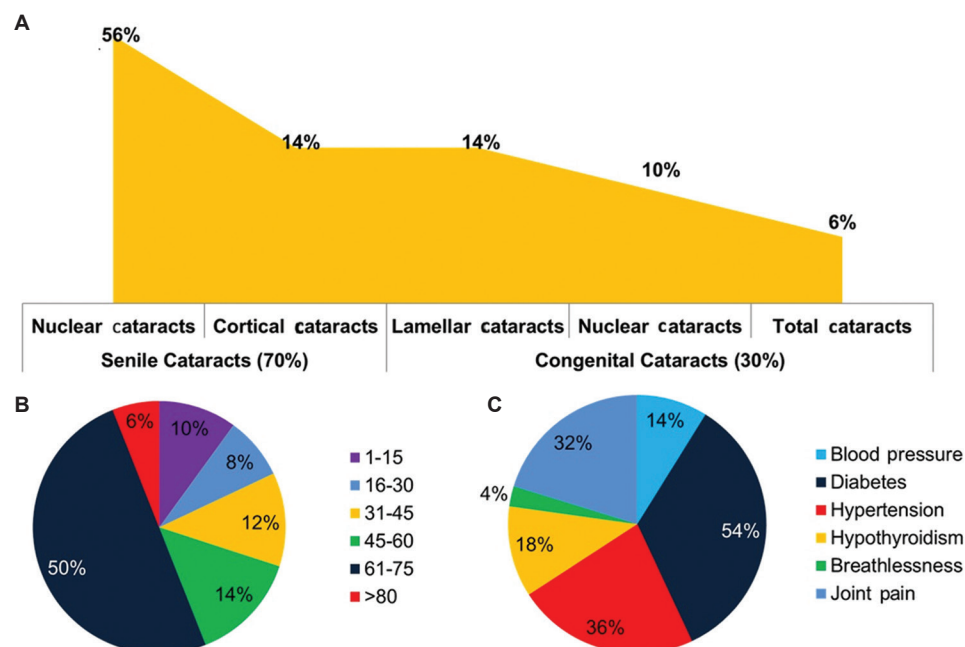


Figure 1. (A) Different types of cataracts in congenital and senile cases; (B) Distribution of cataract cases across different age groups; (C) Prevalence of associated comorbidities

Control participants were selected from the same hospital setting, specifically individuals visiting for routine medical consultations or minor ailments, ensuring demographic similarity to the cataract patient group. To maintain the integrity of the control group, each participant underwent a thorough screening process to confirm the absence of personal or family history of cataracts, diabetes, or other eye-related conditions. This ensured that the control group remained unaffected by the conditions being studied. Detailed inclusion and exclusion criteria for participant selection are provided in Table 1.

2.3. Sample collection and DNA extraction

Blood samples (2–5 mL) were collected from each participant in ethylenediaminetetraacetic acid (EDTA)-coated vacutainer tubes. The samples were then transported in an ice box to the Molecular Biology Laboratory, Department of Zoology, where they were preserved at -20°C until further processing. Genomic DNA was isolated using the phenol-chloroform method¹¹ with slight modifications and subsequently dissolved in Tris-EDTA buffer.

2.4. Gene amplification, Sanger sequencing, and bioinformatics analysis

After DNA isolation, the study employed pre-designed primer sequences for GJA3 and GJA8 exon 2 (Table 2).¹² These primers were verified for optimal binding efficiency

through *in silico* analysis using the University of California, Santa Cruz (UCSC) Genome Browser's *in silico* polymerase chain reaction (PCR) tool. This step was undertaken to ensure the specificity and technical reliability of the primers used in the study. The size of the amplified products was estimated by agarose gel electrophoresis following PCR (Figure 2A and B).

Following PCR, the amplified products of both genes were purified using the column method (Applied Biosystems, New Delhi) and sequenced bi-directionally on an ABI3730 Automated Sequencer (Applied Biosystems, New Delhi). Clean reads were aligned to the UCSC human reference genome (GRCh37/hg19) using the Burrows-Wheeler Aligner program (version 2.6.6), then compared to the National Center for Biotechnology Information GenBank reference sequences using Chromas software (version 2.6.6) and cross-referenced with reported mutations in the literature.

3. Results

3.1. Demographic and clinical parameters

A total of 100 individuals were enrolled in the study, comprising 50 cataract cases and 50 control subjects. The demographic distribution of these participants by gender and age group is summarized in Table 3. Among the cataract patients, 32 were female (64%) and 18 were male (36%), resulting in a female-to-male ratio of approximately 2:1 (Table 3). Fifteen patients had CCs, and 35 had senile cataracts (Figure 1A). Among the senile cataract cases, nuclear cataracts were the most common ($n = 28$ cases; 80%), followed by cortical cataracts ($n = 7$ cases; 20%) (Figure 1A). Among the CC cases, the most prevalent type was lamellar cataracts ($n = 7$; 46.66%), followed by nuclear cataracts ($n = 5$; 33.33%) and total cataracts ($n = 3$; 20%) (Table 4). The distribution of cataract cases across different age groups (Figure 1B) reflects the diversity of cataract location within the Jammu region of North India. The highest prevalence of cataracts was observed in the 61–75 years age group (50%), as shown in Table 4. Prevalence decreased in both younger and older age groups (Figure 1B). Among associated parameters, diabetes was the most common comorbidity (54%), followed by hypertension (36%) and joint pain (32%) (Figure 1C). These findings highlight the

Table 1. Inclusion and exclusion criteria for participants

Criteria	Details
Inclusion	
Age range	No age limit was applied
Cataract diagnosis	Confirmed cases of cataracts based on history and clinical evaluation
Consent	Signed written informed consent obtained
Exclusion	
Unwilling guardians	Guardians unwilling to provide consent
Steroid use	Patients with a history of steroid use
Radiation therapy	Patients with a history of previous radiation therapy
Laser therapy	Patients with a history of previous laser therapy

Table 2. Details of primer sequences used during the experiment

Gene	Primer set sequences	Product size	Reference
GJA3	Forward 5-GTGCTGCAGATCATCTTCGT-3 Reverse 5-TGCTTCCTCCTTCTCTCTCC-3	668 bp	12
GJA8	Forward 5-AAAGAGAGGGAGGAGGAGGA-3 Reverse 5-GCCCAGTTCTGCTCAGTCAT-3	825 bp	

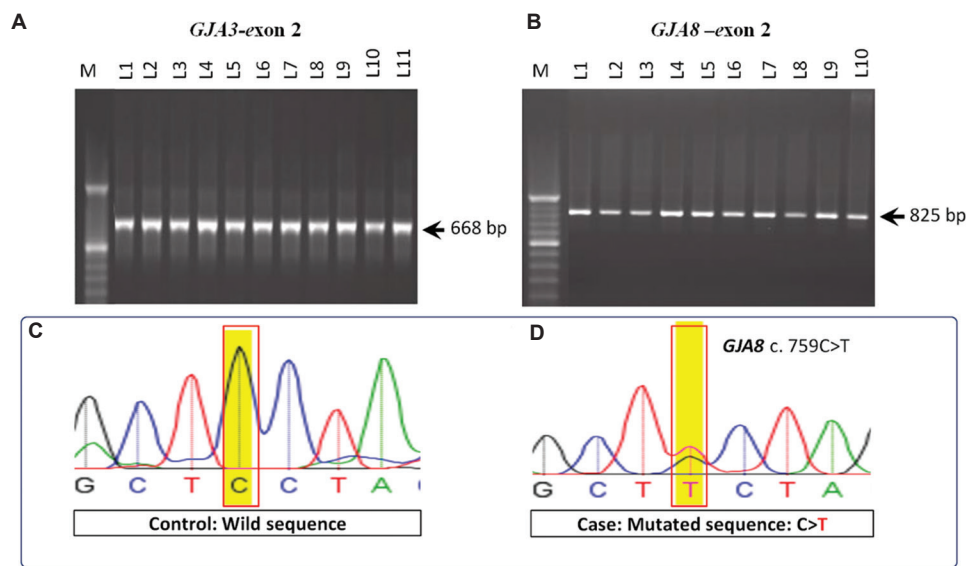


Figure 2. Agarose gel image displaying the amplified product of (A) *GJA3*-exon and (B) *GJA8*-exon 2; Sequence chromatogram (C) Showing no mutations in control samples and (D) illustrating a C>T mutation in cataract patient samples

Table 3. Demographic distribution of cataract cases and controls by gender and age group

Variable	Category	Case		Control	
		<i>n</i>	%	<i>n</i>	%
Gender	Male	18	36	16	32
	Female	32	64	34	68
Age	1–15	5	10	3	6
	16–30	4	8	7	14
	31–45	6	12	11	22
	46–60	7	14	3	6
	61–75	25	50	18	36
	>80	3	6	8	16

significant impact of age and comorbidities on cataract prevalence (Table 1).

3.2. Mutation analysis

3.2.1. *GJA3*-exon 2

No variations in the exon 2 segment of *GJA3* were detected among cataract patients. However, previous studies have reported multiple mutations in *GJA3* associated with different types of cataracts (Table S1). The absence of such variations in our cohort may be attributed to differences in genetic architecture across populations or the influence of population stratification. Given that genetic variations often exhibit population-specific patterns, it is possible that mutations in *GJA3* linked to cataracts are more prevalent in certain ethnic groups while being absent or rare in others.

Table 4. Clinical presentation among cataract cases

Variable	Category	Cataract cases (<i>n</i> =50)	Percentage
Senile cataracts (70%; <i>n</i> =35)	Nuclear cataracts	28	56
	Cortical cataracts	7	14
	Lamellar cataracts	7	14
Congenital cataracts (30%; <i>n</i> =15)	Nuclear cataracts	5	10
	Total cataracts	3	6
Age	1–15	5	10
	16–30	4	8
	31–45	6	12
	46–60	7	14
	61–75	25	50
	>80	3	6
Comorbidity	Blood pressure	7	14
	Diabetes	27	54
	Hypertension	18	36
	Hypothyroidism	9	18
	Breathlessness	2	4
	Joint pain	16	32

3.2.2. *GJA8*-exon 2

Regarding the second gene, *GJA8*, a novel variation, c.759C>T (p.Leu268Leu), was identified in four individuals with CCs. This heterozygous synonymous mutation, also known as a silent mutation, was absent in the control group (Figure 2C and D). The affected individuals exhibited lamellar cataracts and total CCs, suggesting a possible

association between this mutation and these phenotypes. The variation, RefSNP: rs3766503, has not been previously reported in other studies. Although synonymous mutations do not change the protein sequence, they can still disrupt gene function by affecting splice sites, creating new splice sites, or altering splicing regulatory elements, such as exonic splicing enhancers or silencers. These alterations can lead to outcomes, such as exon skipping or partial exon deletions.

Sequence alignment and cross-species conservation analysis confirmed the high conservation of leucine at position 268 across eight species, including humans, mice, dogs, and elephants (Figure 3A and B), highlighting its functional importance despite the synonymous nature of the variation. Meanwhile, *in silico* analysis predicted the GJA8 mutation p.Leu268Leu to be benign (1-147908759-C-T | gnomAD v4.1.0 | gnomAD) (Figure 3C). Following the laboratory work, a follow-up visit with the patients carrying the mutation revealed no family history of

cataracts, suggesting the mutation might not be directly linked to hereditary cataract development.

4. Discussion

Cataracts, the leading cause of blindness worldwide, arise from a combination of environmental and genetic factors, with genetic predisposition playing a particularly significant role. Mutations in exon 2 of gap junction genes, such as GJA3 and GJA8, which are essential for maintaining lens transparency, have been implicated in cataractogenesis.^{3,5,6} This study focused on examining exon 2 of these genes in cataract patients from North India to identify potential pathogenic mutations. Identifying such genetic variants is critical for improving diagnostic accuracy, assessing individual risk, and guiding the development of targeted therapeutic strategies.

Regarding the first gene of interest, GJA3, no variation was detected in exon 2 among the North Indian cataract patients analyzed in this study. However, comparative

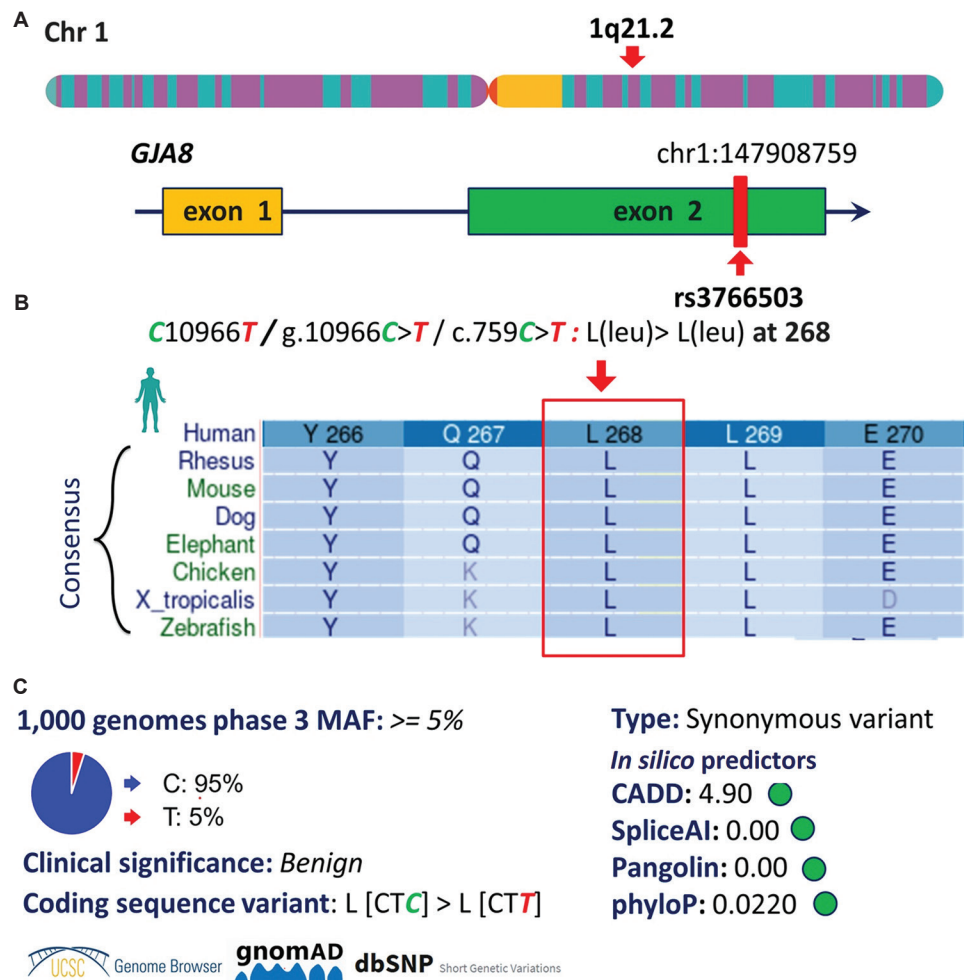


Figure 3. (A) Location of the GJA8 gene on chromosome 1 (1q21.2); (B) Structural representation of the GJA8 gene, highlighting exons and introns; (C) Features of the C>T mutation in the GJA8 gene, showing the nucleotide change and its position within the gene

analysis with previous studies across various ethnic groups reveals that inherited cataracts have been associated with several mutations in *GJA3*. These include missense mutations linked to different cataract phenotypes, such as zonular pulverulent, ant-egg lamellar, variable total, and nuclear types. Notable examples include p.D3Y,¹³ p.L11S,¹⁴ p.V28M,¹⁵ p.R76G,¹⁵ and p.W45S.¹⁶ Moreover, recurrent mutations, such as p.V44M^{17,18} and p.D47N,^{19,20} have been reported in both Asian and Caucasian populations, suggesting the presence of mutational hotspots within the gene. In addition, several variations in *GJA3* have been found to cluster in the C-terminal domain and are primarily associated with pulverulent cataract phenotypes. These include mutations, such as p.P187L,²¹ p.P187S,²² p.N188T,²³ and p.N188I.²⁴ Multiple studies have identified different *GJA3* variants across various ethnic populations, including Hispanic,¹³ Indian,^{25,26} Chinese,^{27,28} Danish,¹⁴ and Australian cohorts.²⁹

Notably, this is the first study to investigate *GJA3* in the context of cataracts within the North Indian population, offering valuable insights into the genetic landscape of cataractogenesis in this region. However, the present analysis was limited to exon 2, and it is plausible that mutations in other exonic or regulatory regions of *GJA3* may contribute to cataract susceptibility. Therefore, comprehensive investigations involving whole-gene sequencing and functional validation studies are warranted to fully elucidate the role of *GJA3* in ocular development and its potential involvement in CCs. Expanding the study to include larger, ethnically diverse cohorts will further clarify the significance of *GJA3* mutations in cataract development within and beyond the North Indian population.

Concerning the second gene, that is, *GJA8*, a novel synonymous variation, c.759C>T (p.L268L), was identified in four affected individuals presenting with lamellar and total CCs. *In silico* predictors showed the benign nature of the variation (Figure 3C). The *GJA8* gene encodes Cx50, a transmembrane connexin protein essential for lens growth and the maturation of lens fiber cells (*GJA8* Gene - GeneCards | CXA8 Protein | CXA8 Antibody). The encoded protein is a key component of gap junction channels, which facilitate intercellular communication and function in a calcium- and pH-dependent manner.^{30,31} These gap junctions contribute to lens homeostasis by providing an intercellular pathway crucial for the internal microcirculation of the lens, and they play an essential role in maintaining lens transparency.^{32,33} Connexin50 has also been implicated in cell proliferation and the regulation of lens size.³⁴ However, to fully understand the potential functional impact of the identified mutation on protein function, further analysis is required. This could

include *in vitro* or *in vivo* studies to assess whether this synonymous mutation could subtly affect the protein's structure or function.

When comparing our results with those of other studies, several mutations have been reported across distinct populations with different types of cataracts. For example, in an Iranian family, c.68G>C was linked to progressive dense nuclear cataracts.³⁵ In Indian families, c.131T>A and c.134G>C were associated with cataracts with microcornea.³⁶⁻³⁸ Other instances from India include c.593G>A, linked to posterior subcapsular cataracts;³⁶ c.905T>C, linked to zonular cataracts;³⁹ and c.670insA, linked to nystagmus and complete cataracts.⁴⁰ Other ethnicities have also been represented, including a Russian family with zonular pulverulent cataracts,⁴¹ a German family with triangular nuclear cataracts,⁴² and a Danish family with nuclear cataracts and microcornea¹⁴ carrying c.565C>T. In addition, a Chinese family with pulverulent nuclear cataracts revealed c.827C>T,⁴³ a Pakistani family with zonular nuclear pulverulent cataracts revealed c.142G>A,⁴⁴ and an English family with zonular pulverulent cataracts revealed c.262C>T⁴⁵ (Table S2).

In summary, the present study reports the first association of a *GJA8* mutation with autosomal recessive inheritance in CCs within the North Indian population. CCs, which account for approximately 14% of global cases,⁴⁶⁻⁴⁹ are classified into various subtypes based on their shape and anatomical location.³ They exhibit significant genetic and phenotypic heterogeneity, with more than 200 loci and 100 genes implicated in their development.^{3,50} In addition to the mutation identified in our study, multiple variations have been reported in different genes. Mutations in crystallin genes, such as *CRYAA*, *CRYAB*, *CRYBA1*, *CRYBB1*, *CRYBB2*, and *CRYBB3*, account for nearly half of the known pathogenic variants.⁵¹ Such genetic architecture reflects the complexity of CCs, with approximately 22.3% of cases in children being inherited. Among these, autosomal dominant inheritance is the most prevalent pattern, although autosomal recessive and X-linked forms have also been reported.⁵²⁻⁵⁵ Therefore, genetic studies are essential for understanding the molecular mechanisms of cataractogenesis, as different mutations can lead to varied lens morphologies, while similar clinical presentations may result from distinct genetic alterations.⁵⁶⁻⁵⁹ This complexity underscores the significance of genetic research in unraveling the mechanisms and inheritance patterns of CCs. Thus, it can be concluded that the development of cataracts, whether during infancy or later in life, reflects a combination of factors, including the accumulation of biomolecular damage and the presence of pathogenic sequence variants.⁶⁰

5. Strengths, limitations, and future perspectives of the study

This study presents significant strengths, notably a balanced case-control design and the identification of a novel synonymous variation in the *GJA8* gene (c.759C>T), which contributes valuable data to the limited understanding of CCs in the North Indian population. Bioinformatics analysis further emphasizes the potential importance of this mutation, showing high evolutionary conservation of the leucine residue across multiple species.

However, the study has several limitations. First, the relatively small sample size may have reduced statistical power, limiting the generalizability of the findings. Moreover, only exon 2 of the *GJA3* and *GJA8* genes was analyzed, which may have excluded other pathogenic variants located in additional exons, intronic regions, untranslated regions, or regulatory elements. In addition, other cataract-associated genes were not examined, limiting the scope of the genetic analysis. Although the identified synonymous mutation was predicted to be benign, no functional validation was performed, leaving open the possibility of subtle effects on splicing or gene regulation. The absence of segregation or pedigree analysis further limits our understanding of whether the variant is *de novo* or inherited.

Future research should include functional assays, such as minigene splicing analysis and expression profiling to evaluate the impact of the identified variant at the transcript and protein levels. In addition, family-based studies are essential to understand the inheritance pattern and penetrance of the mutation. Broader genomic approaches, such as whole exome sequencing or whole genome sequencing, should be employed to uncover variants beyond the analyzed exon, including those in regulatory and non-coding regions. Addressing these gaps will be crucial in advancing our understanding of cataract genetics.

6. Conclusion

This study examined cataracts in the Jammu region, focusing on the exon 2 segments of *GJA3* and *GJA8*. No polymorphisms were detected in exon 2 of *GJA3*, suggesting that this region may not contribute to cataractogenesis in this population. However, a novel synonymous mutation, c.759C>T (p.Leu268Leu), was identified in *GJA8* among four individuals with CCs. Despite its benign prediction and lack of familial history, its association with specific cataract subtypes warrants further investigation. These findings highlight the need for additional genetic studies to better understand cataract development.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Parvinder Kumar, Pooja Devi

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Writing – original draft: Pooja Devi

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Ethics approval and consent to participate

This hospital-based case-control study was conducted following approval from the Institutional Ethics Committee of Government Medical College, Jammu (Letter number: IEC/GMC/2022/1091), as well as the Ethical Committee of the University of Jammu (Letter number: DRS/22/4957). Participant recruitment was carried out between June 2020 and September 2021. As the study involved patients with congenital cataracts, written informed consent was obtained from their guardians before inclusion. Data were obtained after receiving written informed consent from each study participant.

Consent for publication

Not applicable.

Availability of data

The data analyzed in the present study are unavailable to the public due to privacy concerns. Inquiries should be directed to the corresponding author.

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