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Identification and Segregation Analysis of LCA5 Variants in Two Pakistani Families with Leber Congenital Amaurosis

Asima Saman[1]*, Muhammad Ali Waryah[2], Muhammad Asif Naeem[1,3]* and Kausar Malik[1]

[1]*Center of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan*
[2]*Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan*
[3]*Centre for Applied Molecular Biology, University of the Punjab, Lahore, Pakistan*

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Key words
Leber congenital amaurosis, *LCA5*, Lebercilin, Retinal dystrophy

ABSTRACT

Leber Congenital Amaurosis (LCA) (OMIM: 204000,604537) is a severe inherited retinal dystrophy characterized by early-onset vision loss and photoreceptor dysfunction. Mutations in the *LCA5* gene (HGNC ID: 31923), encoding the ciliary protein Lebercilin, have been associated with disrupted photoreceptor function. This study reports the segregation and *in silico* analysis of two pathogenic *LCA5* variants NM_001122769.3, NP_001116241.1 p.(Pro384Glnfs*18) and p.(Gln479Profs*16)) identified in two independent Pakistani families, LUPCG18 and LUVI-31, affected by LCA. Pedigree analysis confirmed autosomal recessive pattern of inheritance, and variant pathogenicity was supported by bioinformatic tools. Structural modeling revealed loss of three hydrogen bonds for p.(Gln479Profs*16) followed by early protein truncation, suggesting structural destabilization and loss of function for Lebercilin. Hence, our findings expand the mutational spectrum of *LCA5* and highlight its role in the pathogenesis of *LCA* within the Pakistani population.

INTRODUCTION

Leber Congenital Amaurosis (LCA) is a severe, early-onset retinal dystrophy characterized by profound visual impairment from birth along with nystagmus and abnormal electroretinogram (ERG) responses (Munir *et al*., 2024). LCA primarily affects photoreceptors, has a prevalence ranging from 1 in 372 in certain rural South Indian populations to 1 in 9000 in Korea (Tehreem *et al*., 2022). Though this prevalence varies globally, LCA remains a significant cause of inherited childhood blindness worldwide (Sato *et al*., 2020). Approximately, 5% of all inherited retinal dystrophies (IRDs) are caused by LCA and is considered to be the most severe form (Skorczyk-Werner *et al*., 2023). The genetic etiology of LCA is highly heterogeneous, with mutations in over 28 genes reported till now to be associated with the LCA phenotype, showing the complex genetic landscape underlying this condition (Tareen *et al*., 2025). Among these genes, *LCA5*, encoding the centrosomal protein lebercilin, is associated with the severe form of LCA associated with its mutations (Skorczyk-Werner *et al*., 2023). Lebercilin, a ciliary protein, is widely expressed in ciliated epithelia throughout the body however, mutations in *LCA5* typically result in a retinal dysfunction in humans (Faber *et al*., 2023). In the mouse retina, *Lca5* mRNA expression increases during development within photoreceptor cells, indicating specialized early stage function of Lebercilin in these cells (Faber *et al*., 2023).

The *LCA5*, encoding the lebercilin protein is essential for outer segment maintenance and photoreceptor survival (Den Hollander *et al*., 2007, 2008). Mutations in *LCA5* disrupt ciliary transport mechanisms hence, causing photoreceptor dysfunction and degeneration (Jacobson *et al*., 2009; Mackay *et al*., 2013). Although *LCA5* mutations are a rare cause of LCA globally, their incidence and mutation spectrum in the Pakistani population remain understudied.

This study describes the identification and detailed segregation analysis of two *LCA5* frameshift variants NM_001122769.3 c.1435dupC p.(Gln479Profs*16) and c.1151delC p.(Pro384Glnfs*18) segregating in two

* Corresponding author: asima.saman@cemb.edu.pk, asif.naeem@cemb.edu.pk
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unrelated Pakistani families, LUVI-31 and LUPCG18 respectively. Using genetic, bioinformatic, and protein structural analyses, we provide evidence supporting the pathogenicity of these variants and their role in LCA related disease etiology.

MATERIALS AND METHODS

Study participants and clinical evaluation

This study was approved by the ethical committee of National Centre of Excellence in Molecular Biology, University of the Punjab, Lahore. Two unrelated Pakistani families, LUPCG18 and LUVI-31, were recruited from the Sindh province of Pakistan. Both families presented with vision impairment (HP: 0001133), nystagmus (HP:0000639), and photophobia (HP:0000613). Comprehensive clinical evaluations were conducted including detailed ophthalmological examinations and systemic phenotypic assessments including skeletal, behavioral and neurological features. Blood samples were taken after the written informed consents were obtained from all participants in accordance with institutional ethical guidelines.

Genetic analysis

Genomic DNA was extracted from peripheral blood samples using the organic extraction method. Whole exome sequencing (WES) was subsequently performed, and variants were filtered based on parameters as outlined previously (Ghaffar *et al*., 2024). Prioritized candidate variants were then validated and segregated in family members through Sanger sequencing.

In silico *analysis and expression study*

The UCSC Genome Browser (Perez *et al*., 2025) and MetaDome protein (Wiel *et al*., 2019) prediction tool were utilized to generate bar diagrams illustrating gene and protein features, respectively. MetaDome was further used to assess the mutation tolerance ratio at specific amino acid positions. PolyPhen-2 (Adzhubei *et al*., 2013) was used to evaluate the conservation scores of both variants. Transcriptomic expression levels in human retinal organoids were analyzed using the UCSC Cell Browser (Perez *et al*., 2025) to identify impacted cell types. Protein-protein interaction analyses, including STRING (Szklarczyk *et al*., 2023) and binary interaction networks (Orchard *et al*., 2014), were performed to identify LCA5 protein-associated interacting proteins involved in disease pathogenesis. For structural insights, 3D protein modeling was conducted by extracting Protein Data Bank (PDB) files from AlphaFold (Jumper *et al*.,2014), followed by analysis with PyMOL to assess effects on hydrogen bonding and overall protein conformation.

RESULTS

LCA5 *variants segregation*

In family LUPCG18, a rare frameshift deletion (NM_001122769.3) c.1151delC, previously reported (Munir *et al*., 2024), was identified (Fig. 1B). This variant occurring in exon 8 of LCA5 leads to premature truncation of Lebercilin in non-structural domain region (Fig. 2A).

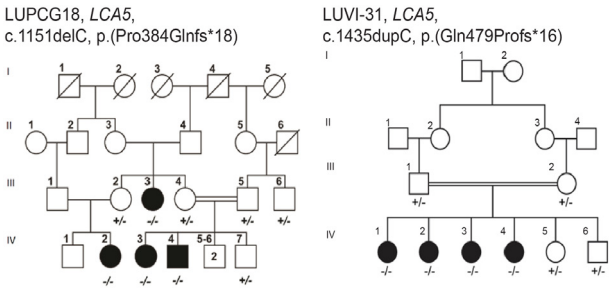

Fig. 1. Homozygous frameshift mutations segregate in two Pakistani families in autosomal recessive pattern.
(A) Pedigree of the LUPCG18 family showing segregation for the variant NM_001122769.3 c.1151delC (p.Pro384Glnfs*18). (B) Pedigree of the LUVI-31 showing segregating of the variant c.1435dupC (p.Gln479Profs*16). Black Filled symbols indicate affected individuals, while white symbols represent unaffected family member. The squares represent males while the circles represent females of each family, the diagonal line on any of these shows deceased individuals. Double line between male and female represent consanguineous marriage. Genotypes below symbols show the LCA5 variant status (+/+; homozygous wild type, +/-; heterozygous carrier, -/-; homozygous mutant).

Similarly for family LUVI-31, a novel variant (NM_001122769.3) c.1435dupC was segregated with the disease in an autosomal recessive pattern (Fig. 1A). The variant occurs in exon9 resulting into a frameshift mutation causing a premature protein truncation in a non-structural domain of the protein (Fig. 2A). Hence, both variants were homozygous in affected individuals and heterozygous in unaffectedcarriers,supportingrecessiveinheritance(Fig.1A).

Bioinformatics analysis for variant pathogenicity

MetaDome scores for the mutant amino acid variation point to be tolerant with the score of 1.18 for p.(Pro384Glnfs*18) and 1.39 for p.(Gln479Profs*16) (Fig. 2B). However, PolyP100 predicts both mutations to be damaging with extremely rare population allele frequency (Table I).

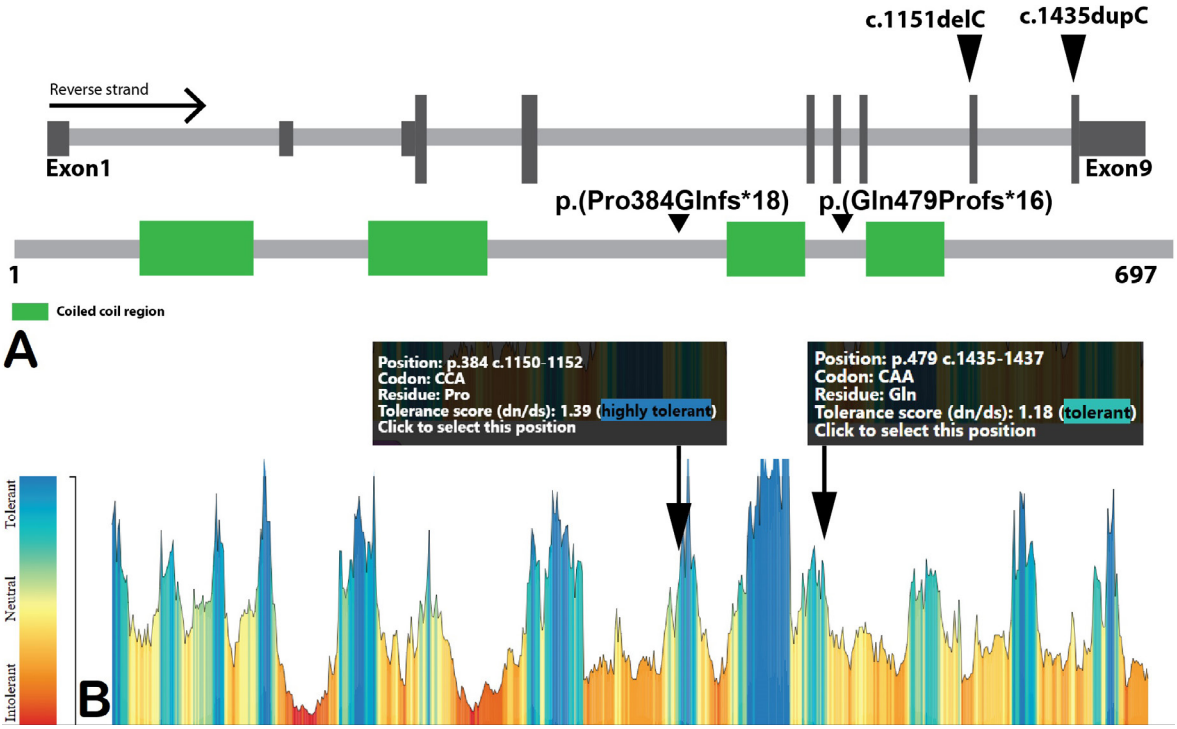

Fig. 2. Genomic structure and mutation tolerance of the *LCA5* gene.
(A) Schematic representation of the *LCA5* gene (NM_001122769.3) showing 9 exons (left to right exon1 to 9) organization and position of organization and position of identified variants c.1151delC and c.1435dupC in exons 8 and 9 respectively marked by black arrowheads. The lower bar shows LCA5 linear protein structure having 697 amino acids, green boxes show coiled coil regions however gray bar area represent non-structural domain regions. (B) MetaDome-based bar graph showing mutation tolerance ratios across the LCA5 protein. Peaks indicate regions with higher tolerance to no tolerance region for amino acid variation (colored blue meaning tolerant, yellow= slightly intolerant and red/orange = highly intolerant). The positions of Pro384 and Gln479 are highlighted, showing both variants reside within relatively tolerant regions, as indicated by their tolerance scores.

Table I. LCA5 variants details in family LUVI-31 and LUPCG18.

Family	LUPCG18	LUVI-31
Gene	*LCA5*	
Accession IDs	NM_001122769.3	NP_001116241.1
cDNA change	c.1151delC	c.1435dupC
Genomic change	NG_016011.1: g.53267del	NG_016011.1: g.54768dup
Protein change	p.(Pro384Glnfs*18)	p.(Gln479Profs*16)
Variant Known	Known	Novel
Exon no.	8	9
Allele frequency (gnomAD)	0.00000399	0
PloyP100	1.197	4.219

3D protein modeling

Protein modeling for p.(Pro384Glnfs*18) does not show any hydrogen bond impact however, as proline is a ringed structure it provides more stability and rigidity to protein site and produces sharp curves for protein folding whereas glutamine has a linear structure and is more flexible amino acid as compared to proline. Hence, this mutation occurs in the loop region of the protein followed by early truncation resulting in structural instability and loss of function (Fig. 3A, B). p.(Gln479Profs*16) on the other hand results in into loss of three hydrogen bonds when Gln479 changes to Pro479. Wild type Gln479 makes two bonds with Asp475, one with each Arg476 and Arg482, respectively, and two with Asn483. When mutation was created from Gln479 to Pro479 a single hydrogen bond of 3.0 Å with Arg476 and two bonds with the length of 3.3 Å and 3.4 Å with Asp475 was lost (Fig. 3 A, C). Also, as described above proline is a more rigid amino acid causing kinks in proteins which can impact protein folding and stability.

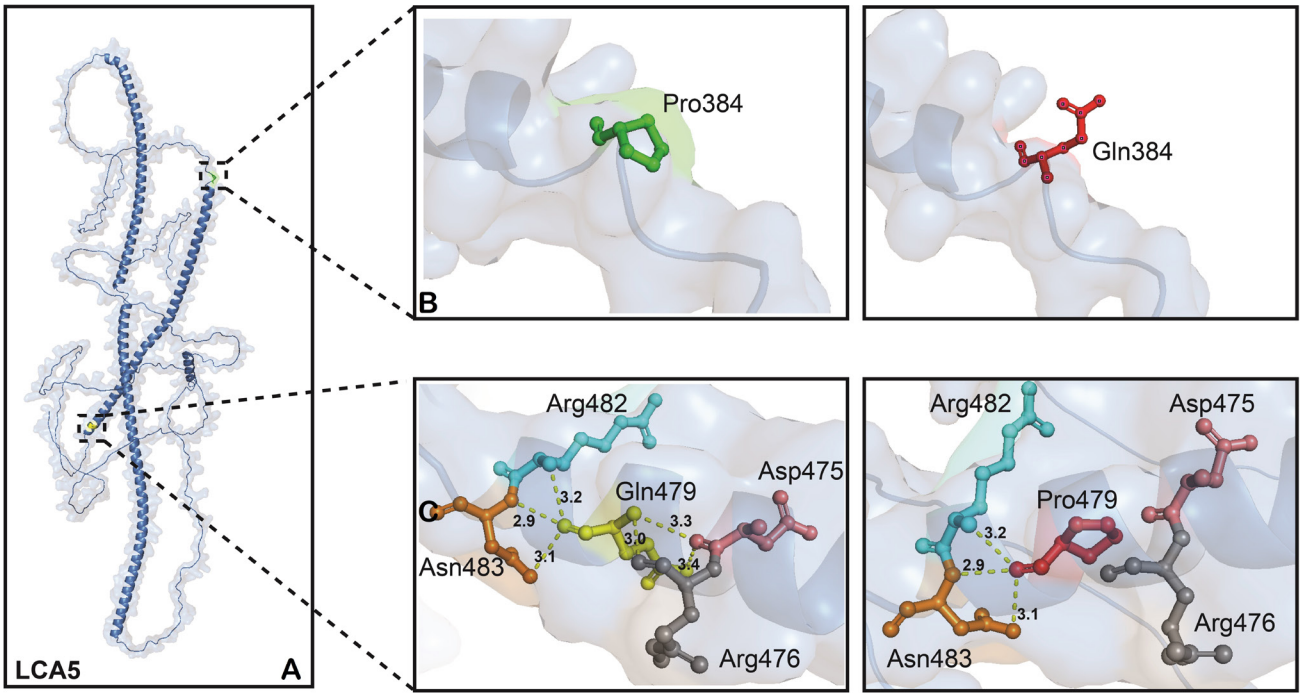

Fig. 3. Structural modeling of LCA5 variants p.(Pro384Glnfs*18) and p.(Gln479Profs*16).
(A) The overall structure of the wild type LCA5 protein with highlighted mutation sites in dashed boxes. (B) Comparative modeling of Pro384 (left box) and Gln384 (right box) reveals that the ringed structure of proline while glutamine confers shows linear structure. Both amino acids form no neighboring hydrogen bond and occur in loop region of the protein. (C) Wild-type Gln479 (left box) forms six hydrogen bonds with Asp475, Arg476, Arg482, and Asn483 respectively. Substitution to Pro479 (right box) leads to the loss of three key hydrogen bonds; one with Arg476 and two with Asp475. Yellow dashed lines show hydrogen bonding between amino acids and values represent bond length of these bonds in Armstrong (Å).

Expression analysis of LCA5 in retinal organoids

Expression analysis was done on dataset of 285,441 single cells from retinal organoids with fully function retinal layers and synapse activation among cells, available at UCSC cell browser. Data shows overall higher expression of *LCA5* in rods, cones, amacrine, retinal pigmented epithelium (RPE) cells, astrocytes and Muller cells (Fig. 4A, B).

Protein-protein interactions

STRING analysis showed major proteins involved in retinal development and function to be interacting with Lebercilin such as RDH12, SPATA7, RD3, AIPL1, RPGRIP1 and USH2A (Fig. 4C). Binary interaction shows a number of proteins involved in LCA phenotype along with LCA5 (Fig. 4D).

DISCUSSION

This study expands the mutational landscape of *LCA5* by providing evidence of two pathogenic frameshift variants NM_001122769.3 c.1151delC (p.Pro384Glnfs*18) and c.1435dupC (p.Gln479Profs*16), segregating in two unrelated Pakistani families LUPCG18 and LUVI-31 diagnosed with LCA. Both variants were found to be causative for the disease in an autosomal recessive pattern of inheritance as shown through pedigree analysis (Fig. 1).

Our findings align with previously reported mutations and their phenotype are consistent with previous reported individuals carrying mutations in *LCA5* showing phenotype of vision impairment (HP:0001103), nystagmus (HP:0000639), and photophobia (HP:0000613) (Corton *et al*., 2014; Den Hollander *et al*., 2007; Li *et al*., 2009; Mackay *et al*., 2013; Zobor *et al*., 2023). The identification of a novel variant (c.1435dupC) highlights the need for further population-based screening to help identify more mutations in *LCA5* causative for LCA.

Frameshift mutations, similar to those identified in our study, usually result in premature truncation of the Lebercilin protein and loss of normal function (Ramprasad *et al*., 2008). Our Protein modeling and *in silico* analyses predicted that LCA5 protein variants p.(Pro384Glnfs*18) and p.(Gln479Profs*16) disrupt protein stability and folding, either due to absence structurally functional

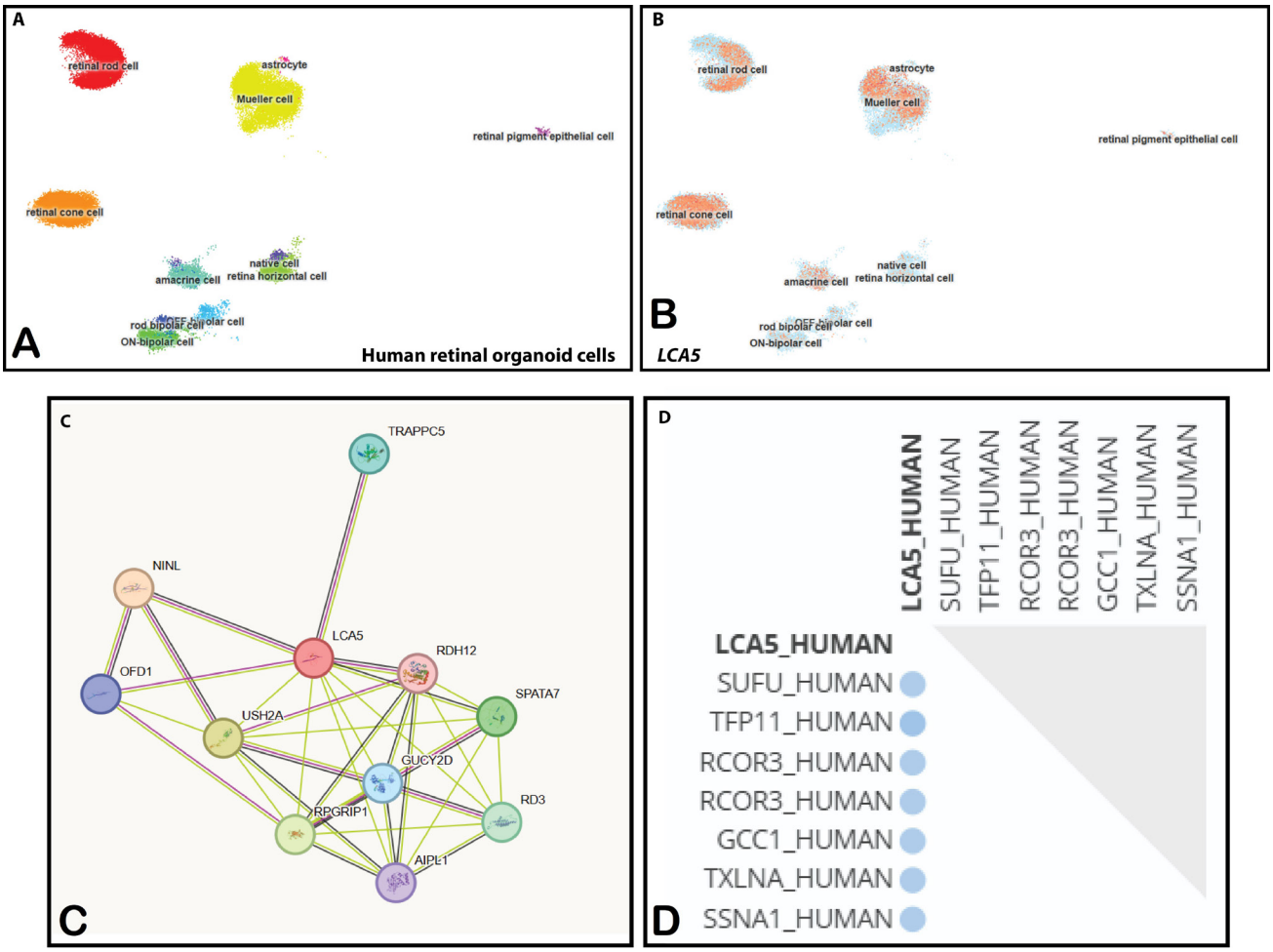

Fig. 4. Expression profile and interaction networks of *LCA5* in the retina.
(A) Clusters of annotated human retinal organoid cell types (n=285,441) visualized using single cell transcriptomic data. (B) Expression of *LCA5* across major retinal cell populations of human retinal organoids, with high signal (orange color) detected in retinal rod and cone photoreceptors, Müller glia, astrocytes, bipolar, amacrine, horizontal, and retinal pigment epithelial (RPE) cells. Blue color represent absence of *LCA5* expression in cells. (C) STRING-based protein-protein interaction network showing LCA5 and its interactions with other IRDs proteins. (D) Binary interaction analysis identifying direct protein partners of LCA5 using multiple annotation databases; core interactors are listed alongside LCA.

regions or by altering amino acids responsible for hydrogen bond formation like for variation p.(Gln479Profs*16) three essential hydrogen bonds were lost in protein helical structure, while proline substitutions leads to cause local rigidity and kinks within the mutant LCA5 protein structure.

Mutation tolerance scores from MetaDome show mutant amino acid regions to be tolerant to amino acid changes (Fig. 2) however, the conservation analyses with PolyPhen-2 supported the likely deleterious nature of these variants (Table I), predicting their evolutionary constraint to LCA5 loci and supporting their pathogenicity to cause disease.

These structural disruptions impair Lebercilin's function at the photoreceptor connecting cilium, disrupting protein trafficking essential for outer segment maintenance and phototransduction (den Hollander *et al*., 2007). Loss of Lebercilin thus leads to photoreceptor degeneration characteristic of *LCA5*-related LCA. Accurate variant identification supports patient stratification for emerging gene augmentation therapies, such as AAV-delivered *LCA5* replacement vectors in preclinical development, and antisense oligonucleotide approaches to mitigate nonsense-mediated decay (Faber *et al*., 2023; Russell *et al*., 2022; Collin *et al*., 2012).

Single-cell transcriptomic profiling of human retinal

organoids shows significant high RNA expression of LCA5 across all major retinal cell types, including rods, cones, RPE, astrocytes, and Müller cells (Fig. 4A, B). These results align with the previous studies highlighting Lebercilin's predominant role in photoreceptor maintenance and ciliary function (Li *et al*., 2025). Most people with Lebercilin mutations only show symptoms in the eyes, even though the protein is found throughout the body, this is likely because Lebercilin is especially critical for developing and maintaining ciliary function in retina (Den Hollander *et al*., 2007).

Interaction network analyses using STRING revealed extensive protein-protein interaction clusters, with LCA5 associated with other essential retinal dystrophy proteins such as RDH12, RPGRIP1, AIPL1, and USH2A (Fig. 4C, D). Disruption of these networks due to mutations could affect retinal structure and function.

According to Leiden Open Variation Database (LOVD) 100 different variants are reported till date, predominantly frameshifts and nonsense mutations causing loss of function for *LCA5*. The identification of a LCA5 novel variant p.(Gln479Profs*16) identified in this study signifies the need and importance of screening such genes with time to identify new genetic mutations, especially in underrepresented populations.

However, this study lacks functional characterization of the identified variants, and future studies are required to prove their actual pathogenicity.

Summary

This study identified two pathogenic frameshift variants in LCA5 in Pakistani families affected by LCA. Both variants, c.1151delC and c.1435dupC (NM_001122769.3), co-segregate with autosomal recessive inheritance and cause early-onset vision impairment (HP:0001103), nystagmus (HP:0000639), and photophobia (HP:0000613). Both the variants were predicted to be causing functional loss of protein through in silico analysis. Overall, this study not only expands the known *LCA5* mutational spectrum but also demonstrates the value of combined clinical, genetic, and *in silico* approaches for variant interpretation. Hence, these findings support future genotype-driven diagnostic and therapeutic strategies in IRDs.

DECLARATIONS

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IRB statement

This study received approval from the Institutional Review Boards at the National Centre of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan and Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan.

Ethical statement

This study was approved by the ethics committee of National Centre of Excellence in Molecular Biology, University of the Punjab Lahore (No: IRB-ID/2023), and the informed consent was obtained from guardian of the patients and all participants.

Informed consent statement

Informed consent was obtained from all the individuals involved in the study.

Generative AI and AI assisted technology statement

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

Statement of conflict of interest

The authors have declared no conflict of interest.

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