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Dual Pathogenic Mutations of the *FYCO1* Gene Segregating with Autosomal Recessive Congenital Cataract in a Pakistani Family

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SS and MAN planned the experiments. SS and MAN carried out the lab experiments in a joint facility. MHA evaluated the patients clinically as an Eye specialist/Ophthalmologist. SS, MS and MAN interpreted the results. SS wrote the write-up and illustrated the results.

Key words
Dual mutations, *FYCO1*, Recessive, Congenital cataract, Childhood blindness, Autosomal recessive

ABSTRACT

Congenital cataracts (CC) are a leading cause of preventable childhood blindness, mainly prevalent in populations with high consanguinity rates, such as Pakistan. This study emphasizes the molecular and bioinformatics characterization of *FYCO1* gene mutations linked with autosomal recessive CC in Pakistani families. Sanger sequencing showed two mutations in *FYCO1*: A reported missense mutation c.749G>A (p. Arg250Gln) and a novel frameshift mutation, c.2481insG p. Gln827Alafs*833. c.2481insG p. Gln827Alafs*833 mutation led to truncated FYCO*1* proteins, considerably impairing its role in autophagy and vesicular trafficking. Bioinformatic analyses, comprising protein structure modeling and disorder prediction, demonstrated substantial disruptions in protein stability and function, particularly affecting *FYCO1's* interactions with autophagic components such as *RAB7* and *MAP1LC3*. Protein-protein interaction networks and domain-based mutation analysis further elucidated the functional impact of these mutations. This comprehensive molecular and bioinformatics approach highlights the genetic heterogeneity of CC in Pakistani populations and underscores the critical role of *FYCO1* in maintaining lens transparency. The findings provide valuable insights into the pathophysiology of congenital cataracts and reinforce the significance of genetic screening and bioinformatic tools for early diagnosis and therapeutic approaches.

INTRODUCTION

Cataract is the manifestation of ocular lens opacification (Graw, 2009). Congenital cataracts are considered the most common cause of blindness that can be prevented in children. Population-based studies around the world have shown that the estimated incidence rate of cataracts is 6 per 10,000 children (Wu *et al*., 2016).

Congenital cataract (CC), also known as pediatric cataract, is a tough eye illness that can cause severe vision loss and childhood blindness globally. The diagnosis might be made at birth or within the first year of life (Khokhar *et al*., 2017). It may be congenital or acquired, unilateral or bilateral, and is extremely curable (Sheeladevi *et al*., 2016; Wu *et al*., 2016). As a result, it is critical to test newborns for cataracts. Symptoms of CC include blurred vision, photophobia, double vision, and night blindness (nyctalopia), which result from a low refractive index and reduced lens clarity (Shiels and Hejtmancik, 2021).

CC may harm nerves in the visual development pathway, causing visual deprivation and irreversible bilateral amblyopia (Reis and Semina, 2019; Şekeroğlu and Utine, 2021). Additionally, CC can cause changes in lens architecture, resulting in ocular lens opacity or foggy vision (Shoshany *et al*., 2020). Cataracts begin mainly when there is a buildup of proteins in the lens and the formation of large aggregates that hinder the transmission of visible light by the retina (Wasnik *et al*., 2021). The lens's transparency is directly tied to the correct morphological organization of the lens fiber cells and the deposition of the soluble proteins known as crystallins to keep the refractive index of the lens

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constant. Any alteration of the structure of the lens leads to the opacification of the lens, hence making the variation of the refractive index of the lens (Shoshany *et al*., 2020). Congenital cataracts have been categorized into various subtypes based on genotype-phenotype correlations, meaning that specific genetic mutations are often associated with distinct clinical features or patterns of lens opacity. This classification helps in understanding the underlying genetic cause and predicting the clinical presentation of the disease. Nuclear, lamellar, total, cortical, anterior polar, and posterior polar are some of the types of opacities based on the location and the structural arrangement of the lens (Hoyt and Taylor, 2012). The prevalence of developmental cataracts (after 1 year of age) ranges from 0.32 to 22.9 occurrences per 10,000, while congenital cataract (existing from birth) has a prevalence of 0.63 to 9.74 per 10,000 (Sheeladevi *et al*., 2016). CC has the highest incidence rate in Asia. The causes of CC are idiopathic (62.2%), inherited (22.3%), and non-hereditary (11.5%). Isolated CC made for 62.3% of cases, followed by CC with ocular problems (22.7%) and CC with systemic disorders (17.3%). Unilateral CC makes up 56% of idiopathic CC but only 6% of hereditary CC, while bilateral CC accounts for 56% of hereditary instances (Shoshany *et al*., 2020; Wu *et al*., 2016). Cataracts cause over 39% of blindness worldwide and account for approximately 51% of blindness cases in Pakistan (Dineen et al., 2007).

CC demonstrates significant heterogeneity because of its high divergence and diverse inheritance patterns (Rahi *et al*., 2000). CC is typically inherited as autosomal dominant, recessive, or X-linked (Wasnik *et al*., 2021). Approximately 50-63% of CC cases are idiopathic, while 30% are monogenic with an autosomal dominant pattern (Hansen *et al*., 2009).

Thirty-nine genes or loci cause non-syndromic cataracts. Autosomal recessive CC has been linked to 14 loci, but some genes have yet to be found (Saleem *et al*., 2022). CC is caused by several genes, including *EPHA2 (*OMIM 176946), *GJA8 (*OMIM 600897), *FOXE (*OMIM 601094), *FYCO1* (OMIM 607182), *GCNT2* (OMIM 600429), *AGK* (OMIM 610345), *AKR1E2* (OMIM 617451), *RNLS* (OMIM 609360), *HSF4* (OMIM 602438), *LIM2* (OMIM 154045), *CRYBA1* (OMIM 123610), *LSS* (OMIM 600909), *CRYBB3* (OMIM 123630), and *GA*. *FYCO1* is the most common genotype of CC in Pakistani households (Iqbal *et al*., 2020; Wasnik *et al*., 2021) Previous studies have also demonstrated the involvement of various genetic mutations in Pakistani families with autosomal recessive congenital cataracts, notably including *FYCO1* and others (Chen *et al*., 2017).

The *FYCO1* gene, located at 3p21.31, has 18 coding exons (NM_024513.4) and is essential for lens development and transparency in humans (Iqbal *et al*., 2020). Moreover, the *FYCO1* protein is elucidated as an autophagy adaptor protein and a constituent of the phosphatidylinositol 3 phosphate (PIP3)-binding protein family (Wasnik *et al*., 2021). Several previous studies showed that autosomal recessive CC could be related to variations in the *FYCO1* gene. The mutations associated with *FYCO1* are the most frequent in Pakistani families with cataracts and contribute about 14% to the total genetic load in this population (Li *et al*., 2020). During the process of autophagy, *FYCO1*, an adaptor protein, promotes microtubule plus-end-directed autophagosomes through instantaneous interaction with kinesin motor proteins and autophagosomal membrane components such as *RAB7* and microtubule-associated protein 1 light chain 3 (LC3) PI3P (Nieto-Torres *et al*., 2021; Pankiv *et al*., 2010). In the present study, we discuss the investigation of the *FYCO1* gene mutation in the Pakistani population regarding cases of cataracts. Thus, the molecular analysis identified two pathogenic mutations in the *FYCO1* gene, one is reported missense mutation c.749G>A (p. Arg250Gln) and other one is novel frameshift mutation, c.2481insG p. Gln827Alafs*833. These mutations, which have been linked to cataracts in various global populations, were detected in our cohort. This finding suggests the presence of distinct genetic variations in *FYCO1* within the Pakistani population. It highlights the importance of conducting genetic research across different geographic regions to better understand the role of *FYCO1* mutations in the etiology of cataracts in this area.. This study was conducted to detect causative genes in complex families with CC and to predict the structural and conformational impacts of the mutation on protein activity.

MATERIALS AND METHODS

This project was designed to find out the association of the *FYCO1* gene with cataracts in the population of Pakistani population.

Ascertainment of families

Twenty-five consanguineous Pakistani families with non-syndromic Congenital cataracts were recruited to participate in this study at the Centre of Excellence in Molecular Biology, Lahore, Pakistan. Institutional review boards (IRBs) at the National Centre of Excellence in Molecular Biology gave their approval to this project. Family PKCC286 (Fig. 1) was recruited from the Punjab Province of Pakistan. Blood samples were collected from affected and unaffected family members. A detailed medical history was obtained by interviewing the patients and their family members. Ophthalmological examinations,

including visual acuity assessment (age-appropriate) and external eye examination, were performed at the Rehmatullah Benevolent Trust (LRBT) Hospital and the Ophthalmology Department, Jinnah Hospital Complex, Lahore. Following the principles of the declaration of Helsinki, the participants provided their informed consent.

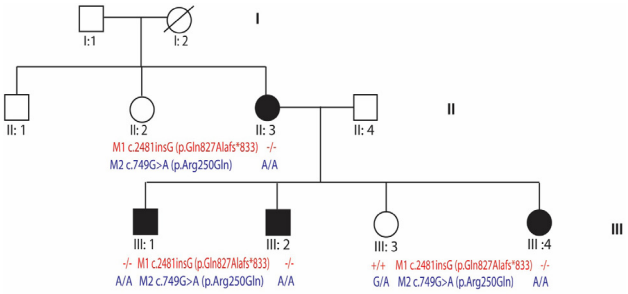

Fig. 1. Pedigree of family PKCC286: The phenotype in pedigree PKCC286 shows the segregation of *FYCO1* mutations associated with autosomal recessive congenital cataracts.

Molecular studies

Blood samples were collected using sterilized syringes and vacutainer (EDTA Vials). DNA was isolated by an o r g a n i c method (Khan et al., 2015). PCR was done with forward and reverse primers to amplify the coding sequence of the *FYCO1* gene. The PCR condition consisted of initial denaturation at 95 °C for 5 min, denaturation at 95 °C for 1 min, annealing at 60 for 1 min, initial extension at 72 °C for 1 min, and a final extension at 72 °C for 5 min. This PCR was set for 30 cycles. 2% agarose gel electrophoresis was done to check the desired DNA band after PCR and its products were mostly cleaned with ethanol precipitation. All PCR products were purified with 95% ethanol. Sequencing of the PCR product was done after purification by Sanger sequencing. Genetic analyzer 3730 (applied biosystems). The sequencing results were analyzed by using Chromas version 2.6.4. Low-quality sequences on both sides were trimmed. All nucleotides were also checked manually to ensure any wrong base call. The NCBI nucleotide blast checked the similarity of the sequence.

Pathogenicity assessment of identified variants

A mutation was considered novel if it was not present in the human mutation database (http://www.hgmd.cf.ac.uk/ac, in the public domain) or the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/index.html, in the public domain) and not in Cat-Map (http://cat- map.wustl.edu, in the public domain). Missense variants were assessed for possible causality with the online programs Sorting Intolerant from Tolerant (SIFT; http://sift.jcvi.org/www/SIFT_enst_submit.html,in the public domain) and polymorphism phenotyping (Polyphen-2; http://genetics.bwh.harvard.edu/pph2/, in the public domain) for protein modeling. The Swiss model is used (https://swissmodel.expasy.org) and chimera (Download UCSF Chimera).

Bioinformatics analysis of FYCO1 *mutations*

For protein order–disorder prediction

The type of disordered *FYCO1* was studied using the PONDR server (https://www.pondr.com/). For other cellular protein interaction studies of *FYCO1*, the String database (https://string-db.org/) was used for earlier known interactions or to predict protein-protein interactions. Cataract-causing mutations in *FYCO1* were performed based on domain-wise locations and mutation type by using the metadome web server (https://stuart.radboudumc.nl/metadome).

RESULTS

FYCO1 *c.749G>A (p. Arg250Gln) variant*

Sanger sequencing chromatograms validate the occurrence of a c.749G>A substitution in the *FYCO1* gene leading to an amino acid change from arginine to glutamine at position 250 (p. Arg250Gln) (Fig. 2). A shows the heterozygous peak, and B, C, and D show the affected, which show a visible A peak. The chromatograms indicate a G to A mutation at nucleotide position 749, where the overlapping peaks in certain panels can imply heterozygosity. The mutation changes the codon, thereby establishing the pathogenic variant and affirming its occurrence in the individuals under test. The substitution may potentially influence *FYCO1* protein function, leading to disease phenotypes, especially those caused by autosomal recessive ocular diseases, such as congenital cataracts.

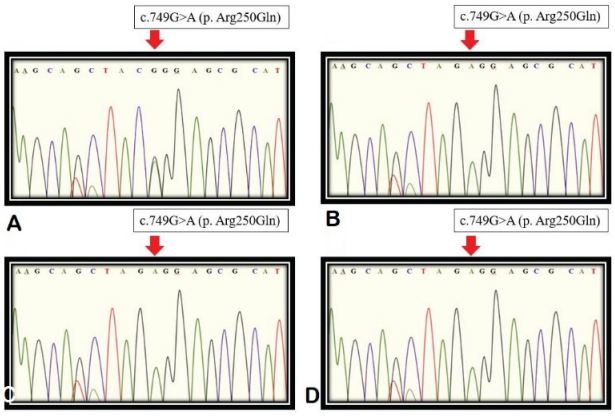

Fig. 2. Sanger sequencing confirmation of *FYCO1* c.749G>A (p. Arg250Gln) variants.

FYCO1 *protein and its interaction with other proteins*

FYCO1 protein has 1478 amino acids including domains in like RUN (49-173 amino acids), Coiled coin (224-1154 amino acids), FYVE (1166-1231 amino acids), LIR (1276-1294 amino acids), and GOLD (1339-1467 amino acids) (Fig. 3A). The RUN domain is impacted by both mutations, but the c.749G>A (p. Arg250Gln) missense mutation interferes with Rab7 binding and autophagosome transport. The FYVE and LIR domains, which are necessary for *FYCO1* function, are removed due to premature truncation caused by the c.2481insG (p. Gln827Alafs*833) frameshift. As a result, autophagy and vesicle transport two essential mechanisms for lens transparency are compromised. Congenital cataracts caused by *FYCO1* dysfunction are associated with both mutations.

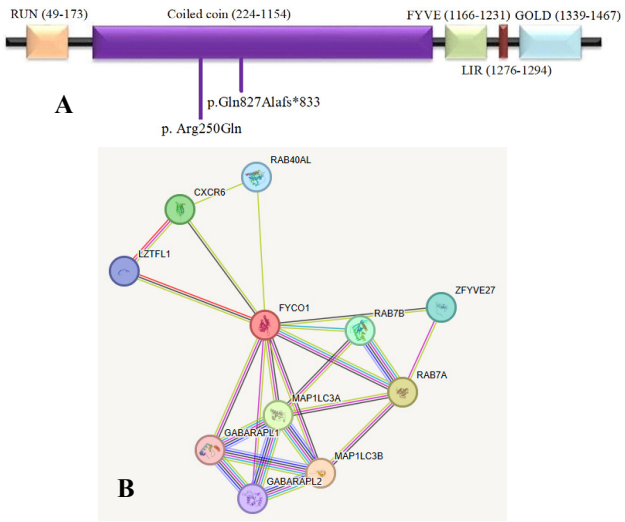

Fig. 3. Domain structure of the *FYCO1* protein (A) and its interaction with other proteins (B).

Protein-protein interaction network for *FYCO1*, a protein involved in vesicular trafficking and autophagy. The central node (*FYCO1*) is shown at the center, indicating its interaction with multiple proteins (Fig. 3B). The network shows various proteins as circles with lines connecting them to *FYCO1* and each other. These proteins include *MAP1LC3A, MAP1LC3B, RAB7A, RAB7B, GABARAPL2, CCZ1B, SASS6, ZFYEVE27, CXCR6, RAB40AL,* and *SASS6*. The edge colors/types indicate interactions, such as physical binding, functional associations, or co-expression. *FYCO1's* interactions with proteins primarily involved in autophagy and vesicular trafficking suggest its crucial role in cellular degradation, vesicle formation, and movement. Mutations in *FYCO1* could disrupt these critical pathways, potentially leading to diseases like congenital cataracts.

Protein structure modeling of FYCO1 *variant*

Figure 4 shows structural modeling of the *FYCO1* protein and the contrast between the normal and mutant proteins brought about by the c.749G>A (p. Arg250Gln) mutation. Panels A and B illustrate the general tertiary structure of the protein in its wild type (A) and mutated (B) form. The replacement of arginine (a positively charged, bulkier amino acid) with glutamine (a polar, uncharged residue) causes changes in folding and potential loss of structural integrity, which can be observed as modifications in the spatial organization. Panels C and D show a close-up view of the site of mutation. In the healthy structure (C), arginine comfortably resides inside the protein core, most likely engaging stabilizing interactions. In the mutant state (D), glutamine is substituted for arginine, potentially disrupting local bonding, influencing helical stability, and possibly disrupting *FYCO1* functional regions. This structural aberration adds to the pathogenic potential of the p. Arg250Gln variant.

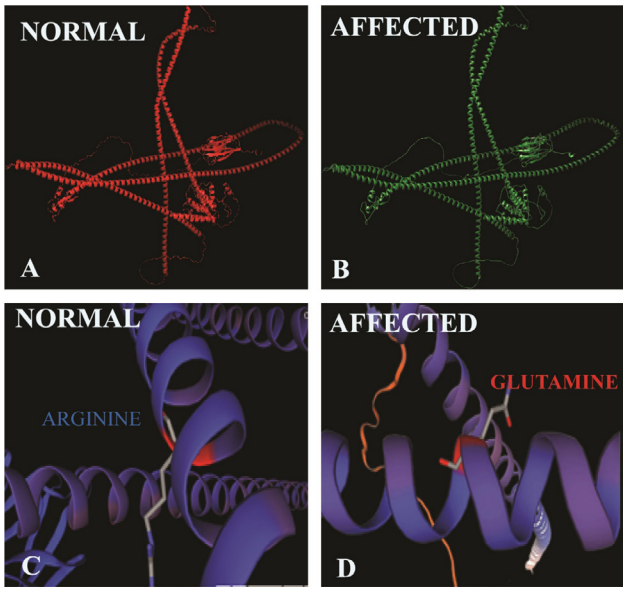

Fig. 4. Structural impact of *FYCO1* c.749G>A (p. Arg250Gln) mutation on protein conformation.

Analysis of disordered region for FYCO1 *variant*

Figure 5A shows the disordered region analysis of the FYCO1 protein by the PONDR server comparing the wild-type (normal) and mutant (affected) due to the c.749G>A (p. Arg250Gln) substitution. Substitution increases disorder in the FYCO1 RUN domain region. The mutant (affected) protein exhibits higher PONDR scores, indicating loss of structural stability at the mutation site. This increased disorder may disrupt Rab7 binding, impairing autophagosome transport.

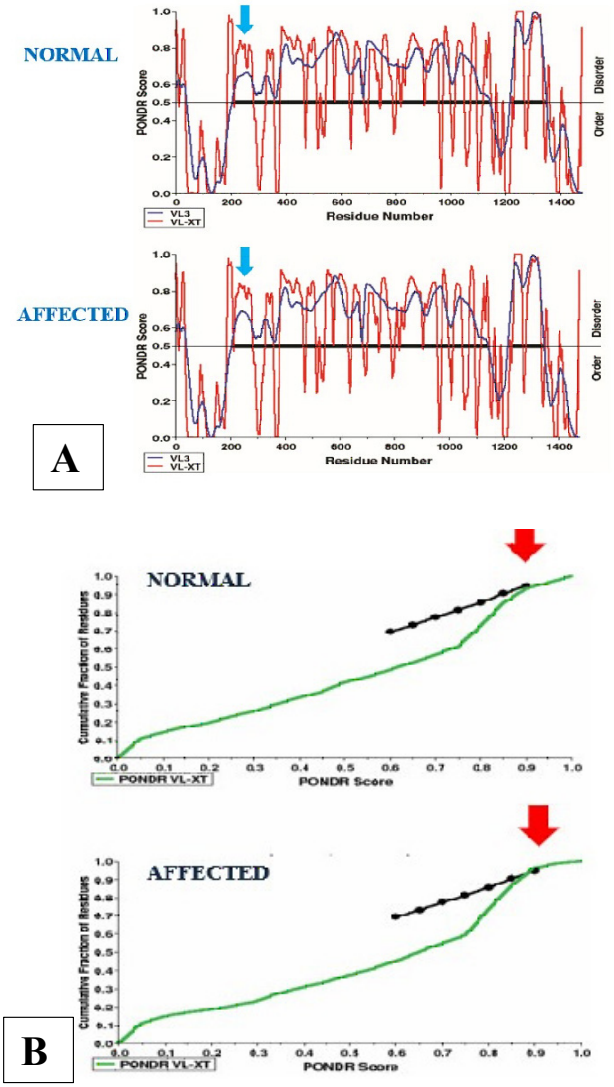

Fig. 5. Disordered regions of *FYCO1* c.749G>A, p. Arg 250G1n after using PONDR server (A), comparison with wild type (B).

Figure 5B shows the disorder levels in wild-type and mutant *FYCO1* proteins using PONDR VL-XT scores. The wild type has fewer disordered residues, suggesting greater structural flexibility. As compared to the mutant shows highly disordered residues, indicating reduced flexibility, which may impair *FYCO1* function in autophagy and vesicle transport.

FYCO1 *mutation c.2481insG p. Gln827Alafs*833*

Figure 6 shows no mutation in homozygous wild type, while samples B, C, and D display clear insertion patterns of G without overlapping, consistent with a homozygous mutant status.

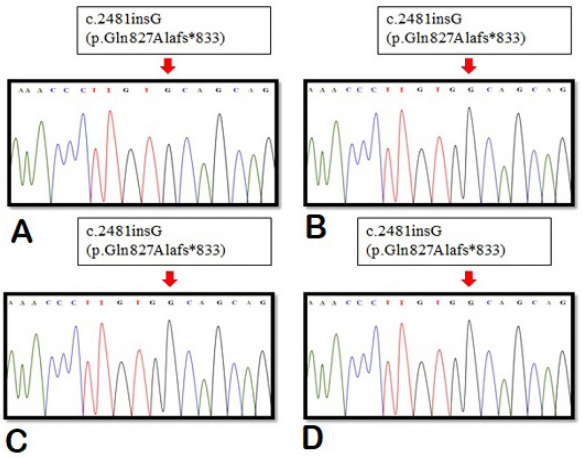

Fig. 6. Sequencing results analysis of *FYCO1* mutation c.2481insG p. Gln827Alafs*833.

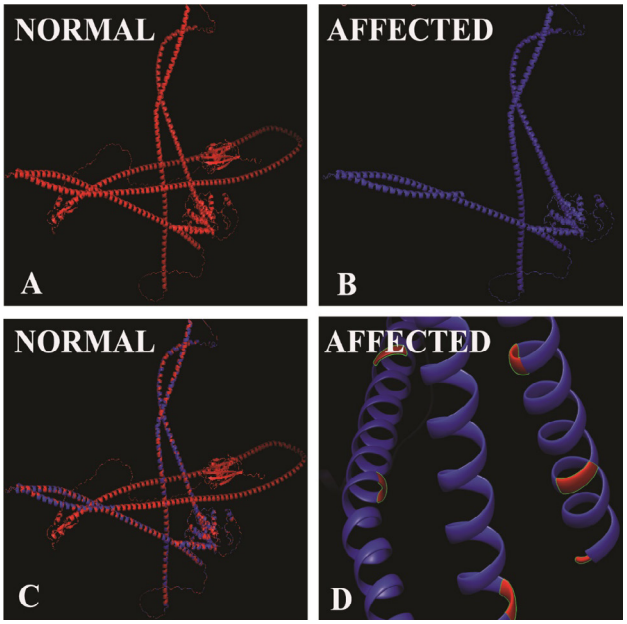

Fig. 7. Protein model structure of *FYCO1* mutation c.2481insG p. Gln827alafs*833.

Figure 7 shows compression of 3D protein model structures of the normal (A) and mutant (B) *FYCO1* c.2481insG p. Gln827Alafs*833 protein (B) by using Swiss model (https://swissmodel.expasy.org/) and Chimera 1.18. The superimposed view (C) highlights noticeable structural deviations caused by the mutation. Panel D zooms in on the affected structure, showing local disruptions (in red), especially in helical regions, indicating loss of structural integrity.

Analysis of disordered region of wild-type FYCO1 *and its mutant*

Figure 8A shows predicted disordered regions in *FYCO1* protein by PONDR for normal (wild type) and mutant (c.2481insG) structures. The first panel is a representation of wild-type protein, indicating a balance of ordered and disordered regions along the entire length of the protein (>1400 residues). The bottom panel, on the other hand, illustrates the mutant (affected) protein, which is truncated because of the frameshift mutation and has a much shorter sequence. Normal genes have 1478 amino acids, and mutant genes have 833 amino acids. The mutant protein has more disorder in some areas, as seen by higher PONDR scores (above the 0.5 threshold line) in all the prediction models (VSL2, VL3, and VL-XT). These alterations suggest that the mutation causes a loss of structural organization, particularly in the C-terminal region of the protein, which could impair *FYCO1's* role in cellular transport and autophagy processes.

Figure 8B The graph shows the cumulative fraction of disordered residues in the *FYCO1* protein by PONDR VL-XT scores for wild-type and mutant forms. Normal has a normal graph but the affected graph shows disordered behavior. It shows how much of a protein is likely to be disordered or flexible. The green line shows the results from a prediction tool (PONDR). A higher score means the protein part is more disordered (less stable). In the normal case, disorder increases steadily, but in the mutant (affected) case, disorder increases suddenly at a later point. The red arrows point to where the biggest change happens. This means the mutation makes parts of the protein behave more unpredictably, which can affect its function.

DISCUSSION

CC represent a major preventable cause of blindness in children and have a strong genetic component, particularly in highly consanguineous populations like those in Pakistan. Using both molecular and bioinformatics methods, this study aims to detect and characterize mutations in the *FYCO1* gene, a known contributor to autosomal recessive congenital cataracts (ARCC). The *FYCO1* gene has previously been shown to be a significant risk factor for CC, especially in Pakistani populations where it accounts for about 14% of the genetic burden linked to the condition (Iqbal *et al*., 2020). This study builds upon the genetic landscape established by Iqbal *et al*. (2020) which identify a missense mutation c.749G>A (p. Arg250Gln). In the current study we identify two pathogenic mutations, one is already reported missense mutation c.749G>A (p. Arg250Gln) and a novel frameshift mutation c.2481insG (p. Gln827Alafs*833). This novel mutation c.2481insG (p. Gln827Alafs*833) improves the growing body of evidence signifying that *FYCO1* plays a fundamental role in the development and maintenance of lens transparency. The bioinformatics analysis in this study provides new perspectives on the structural effects of *FYCO1* mutations. The current study shows that the c.749G>Ap.Arg250G1n and c.2481insG p. Gln827Alafs*833 mutations cause substantial structural disruptions to the *FYCO1* protein, especially in its ability to interact with important autophagy-related proteins like *RAB7* and *MAP1LC3*. We did this by using tools like the Swiss model and chimera for protein modeling. These findings are consistent with the functional roles of *FYCO1 in* autophagy and vesicular transport, as described (Nieto-Torres *et al*., 2021; Pankiv *et al*., 2010).

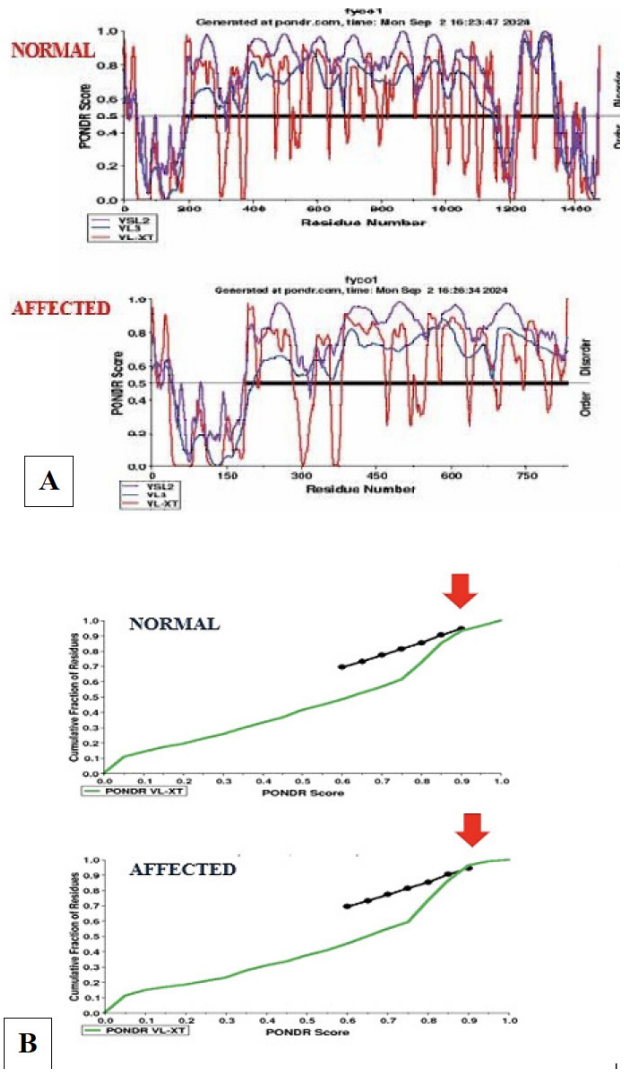

Fig. 8. Disordered regions of *FYCO1* mutant c.2481insG p. Gln827alafs*833 (A), and its comparison with wild-type (B).

Shiels and Hejtmancik (2021) have shown that autophagy plays a crucial role in preserving lens clarity and averting the development of cataracts. This finding is consistent with the current study. Our protein disorder analysis using the PONDR server revealed increased disorder in the mutant proteins, which likely contributes to their reduced stability and impaired function. This is consistent with the findings of Saleem *et al*. (2022) who highlighted the significance of structural stability in the function of *FYCO1* in vesicular trafficking and cellular degradation.

We have identified two pathogenic mutations, one reported mutation c.749G>A p. Arg250G1n and one novel c.2481insG p. Gln827Alafs*833 mutation that profoundly modifies the C- C-terminal region of the protein, specifically affecting domains essential for autophagic function and vesicular transport. According to the structural analysis, this frameshift mutation results in the truncation of important domains, including the LC3-interacting region (LIR) (Nieto-Torres *et al*., 2021) and the FYVE domain, which is involved in phosphoinositide binding. Because of the impaired clearance of damaged proteins in the lens, this disruption most likely inhibits *FYCO1's* ability to mediate autophagosome transport efficiently, which contributes to the formation of cataracts.

The discovery of a novel mutation in this study highlights the genetic pattern of CC in various populations. The c.749G>A, p. Arg250G1n and c.2481insG p. Gln827Alafs*833 mutations, which are specific to this study, raise the possibility that *FYCO1* contains additional population-specific mutations that could add to the genetic burden of CC in Pakistani families.

This is particularly relevant for ocular diseases inherited in an autosomal recessive manner, such as congenital cataracts. The findings of this study support previous conclusions regarding the function of *FYCO1* and provide new insights into the molecular mechanisms underlying congenital cataracts. This work opens the door for future investigations into the precise functional effects of *FYCO1* mutations and the development of targeted therapies for CC by identifying mutation and offering thorough structural analyses.

CONCLUSION

A Pakistani family with autosomal recessive congenital cataracts has two unique pathogenic mutations (c.749G>A (p. Arg250Gln) and c.2481insG (p. Gln827Alafs*833)) in the *FYCO1* gene, affecting the protein's structure and function, particularly in domains involved in autophagy and vesicle transport. This highlights the genetic complexity of congenital cataracts and underscores the importance of thorough genetic screening and structural analysis in understanding inherited cataract causes.

DECLARATIONS

Acknowledgments

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IRB approval

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 Joint collaborative research with NEI/USA & Allama Iqbal Medical Research Centre, Jinah Burn Centre, Lahore, Pakistan.

Ethical statement

The author declare that all data and materials used in this study were obtained and analyzed in accordance with institutional ethical standards. No part of this research involves unethical practices. All ethical principles related to research integrity, confidentiality, and honesty have been strictly followed.

Generative AI and AI-assisted technology statement

The author have declared that generative artificial intelligence (AI) and AI-assisted technologies were not used in the generation of data, analysis, or interpretation of results presented in this manuscript.

Statement of conflict of interest

The authors have declared no conflict of interest.

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