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Mutational Analysis of FOXE3 Gene Causing Cataract in Pakistani Family

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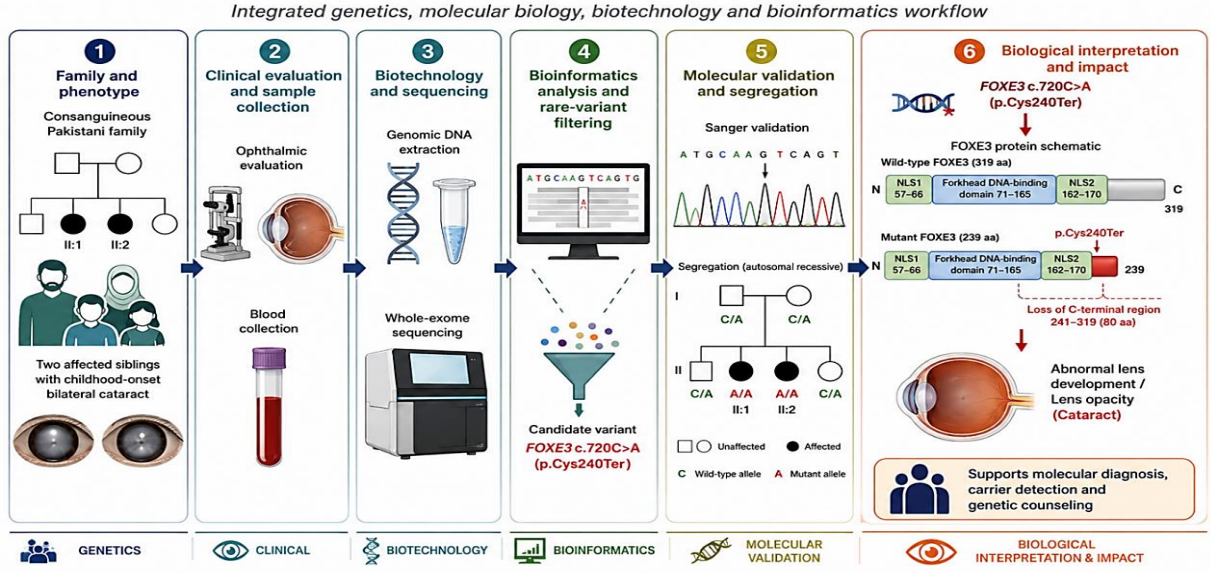
Abstract

The cataracts which is the major cause of blindness in the world has been largely attributed to genetic mutations especially in high consanguinity regions. Particularly, mutation in the FOXE3 genes is found in the congenital cataracts particularly in those families that have had consanguinity marriages. The topic that will be discussed in this paper will be a consanguinity family of Pakistanis and how the FOXE3 gene mutations are used in the pathogenesis of congenital cataracts. Whole-exome sequencing (WES) and DNA analysis identified that two individuals with the disease in the family contained a mutation in the FOXE3 gene (c.720C>A), which produced a premature stop codon at codon 240. The mutation leads to production of a truncated FOXE3 protein that disrupts the lens formation and cataracts are developed. The research will contribute to the knowledge of genetic causes of cataracts and consequent implications early diagnosis, genetic counseling and treatment of the affected patients in consanguineous groups. The findings demonstrate the importance of genetic testing and early intervention in the treatment of congenital cataracts particularly in high-consanguinity areas.



Keywords: Cataracts, FOXE3 gene, Genetic mutation, Congenital cataracts, Consanguinity, Whole-exome sequencing (WES) and DNA analysis.

1. INTRODUCTION

Cataracts rank as one of the most common causes of blindness and poor vision in the entire world and even though majority of the cases are age related cataracts is a significant case of blindness among the kids. One of the complications caused by the opacification of the eye lens which is usually transparent and blocks light to reach the retina therefore makes one have poor vision. Congenital cataracts are also hectic because they may result in severe impairment of visual in case of late diagnosis and treatment. They are either hereditary or environmental because they may be traced to some events like trauma or infection of the pregnant woman but at times there are cases where the cause is genetic (Alhasan *et al.,* 2022; Qasim et al., 2026). It is one of the most important genes that entail the pathology of cataracts in the context of the development and sustenance of the lens in the case of congenital cataracts that is the association of FOXE3, gene that expresses transcription factor. FOXE3 gene mutation has been associated with multiple visual defects such as cataracts, anterior segment malformation and even aphakia which is a condition where the lens has been removed. The process of regulating the expression of the proteins that maintain the transparency of the lens is also associated with FOXE3 gene and the mutations of the gene can result in the appearance of the aggregates of lens proteins that result in the opacification of the lens and the development of the cataract in the end (Alio, 2017; Qasim et al., 2026; Ather et al., 2026).

The cataract formation process is a genetic complex, which comprises of many genes that are being demonstrated as the causes of the less age related and congenital forms of the disease. These genes are important in several processes which are relevant to the activity of the lenses like maintenance of the integrity of the fibers of this lens, intricate transportation of ions as well as proper folding of the crystallin proteins that is crucial to the transparency of the lens. Nevertheless, the current genetic pathogenesis of cataracts has a lot to be learned especially in the consanguinity groups where autosomal recessive hereditary diseases have a higher rate as a result of the high degree of homozygosity of the harmful alleles (Ang *et al.,* 2022). More of the same copy of the recessive alleles is likely to be passed on to the offspring as genetic diseases such as congenital cataracts are commoner in a high consanguinity population, such as in Pakistan. It is also widespread in Pakistan where consanguinity marriage is observed where most of the families are infected by inherited diseases that includes the congenital cataracts. The research of such groups of people may give the priceless information about the genetic determinants of cataracts and contribute to recognizing some new mutations leading to this ailment (Harahap *et al.,* 2022; Qasim et al., 2025).

Cataract has already become an important cause of blindness in Pakistani children and adults. Hereditary diseases such as cataracts congenital have their effects resulting to the high rate of consanguinity in the country (Krall *et al.,* 2018). This has prompted the necessity of genetic research to find out more about the genetic nature of the development of cataracts in the Pakistani families and more so in the families that have a history of consanguinity marriages. Such families can be examined genetically so as to provide the mutations developed behind the formation of the cataract in the attempt to maximize the early diagnosis, genetic counseling and treatment approaches in the affected individuals. One of the main candidates of the genetic mutation research of the cataracts is the FOXE3 gene as this has been found to be of the greatest importance in the initial processes of the lens development. FOXE3 mutation is potentially hazardous and causes various forms of eye problems, including isolated cataracts, and more inhuman diseases like eye problems in other fields i.e. cornea and iris. These mutations are especially encountered in some forms of cataract that are inbred autosomal recessive that are very frequent in the inbreeding communities.

The molecular process through which cataracts develop under an eventuality of the FOXE3 gene mutations is not well understood however it is clear that the gene is central to rendering the lens transparent. FOXE3 helps in regulation of expression of crystallin proteins which form refractive properties of the lens. FOXE3 mutations have the potential to destroy the expression or structure of these proteins which results in the development of cataract as a result of their aggregation. There are numerous mutations in FOXE3 that cause truncation of the protein, which does not have functional domains to carry out normal lens functions. These mutations will probably result into more severe forms of cataracts and premature and accelerated development. The remaining mutations can change the natural shape or functioning of crystallins that result in less severe forms of cataracts that occur later in life. The age and severity of cataracts due to FOXE3 mutation may be highly unreliable, and even within the same family, which implies that there are other genetic/environmental factors that may affect the manifestation of the disease.

The paper under consideration shall attempt to unravel the potential role of the FOXE3 mutations in the progression of the congenital cataracts in a Pakistani family of a consanguinity. The whole-exome sequencing will be carried out to determine the possibility of mutations of FOXE3 gene and it will be compared to the clinical manifestation of cataracts to the ill members of the family. The important aim of the study is to detect new or already known mutations in FOXE3 and the role that the mutations played in the occurrence of cataracts. With the clear mutation identified that causes the development of cataract in this particular family, the genetics involved in the emergence of the disease will be more understood. Also, the proposed findings obtained can be put to use in the enhancement of genetic

counseling and diagnostic treatment among Pakistani and other consanguineous families who have cataracts.

The genetics study on the etiology of cataracts is also significant not only in as far as the molecular cognition of the disease is concerned, but also in the development of improved diagnostic and curative agents. To enhance the excellence of genetic testing, we can seek the genetic mutations that cause cataracts especially when the victims belong to one family and this could be used to make the cataracts be detected earlier and they can be easily controlled. Congenital cataracts can be successfully prevented by early detection of children affected in which it is more beneficial to remove the cataract and replace it with a lens at an early age thus preventing the loss of vision in such children. The afflicted families could also be assisted through genetic counseling to learn the risks of the condition being passed on to the future generations and make good decisions with respect to family planning.

Overall, congenital cataracts are considered as one of the important causes of infant blindness and the pathophysiology of the condition is complicated. The mutations that pertain to the FOXE3 gene are rather in the acquisition of cataracts especially among close relatives. The study will help to create an impression of the cataracts related to FOXE3 in the Pakistani family and acquire knowledge about genetic counseling, early diagnosis, and possible treatment methods that can be applied in the case of the affected individuals. The research can cause a reasonable contribution since the study will not only help in the diagnosis and treatment of cataracts in the targeted families but prevent additional cases of cataract-related blindness in the future due to the presence of some mutations in the FOXE3 gene.

The present study integrates genetics, molecular biology, biotechnology and bioinformatics to investigate the molecular basis of inherited cataract in a consanguineous Pakistani family. Pedigree analysis and segregation testing were used to determine the probable mode of inheritance, while molecular-biological procedures were applied for genomic DNA isolation and Sanger validation. Whole-exome sequencing served as the principal biotechnology platform, and bioinformatics analyses were used to align sequencing reads, identify rare variants, annotate their predicted effects and prioritize variants in genes associated with ocular development. Through this multidisciplinary approach, the study aimed to identify a clinically relevant FOXE3 variant and evaluate its segregation with the ocular phenotype in the investigated family.

2. METHODOLOGY

In research of the genetic causes of cataracts in a single Pakistani family through mutational analysis of the FOXE3 gene was supposed to be conducted. The research approach that will be adopted in this study will be as follows and it will be classified in three groups namely field work, laboratory work, DNA extraction, exome sequencing, and genetic analysis.

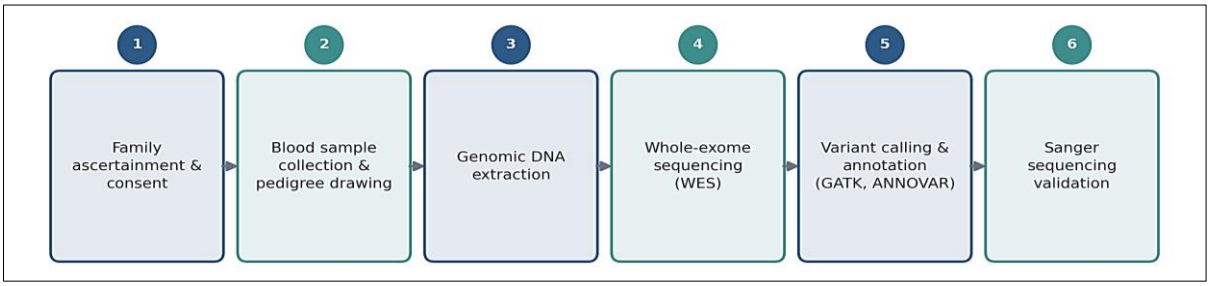


Figure 1.1: Overview of the study workflow used for mutational analysis of the FOXE3 gene, from family ascertainment through Sanger validation

2.1 Preparation of Stock Solutions

2.1.1 Preparation of Stock Solutions.

With the molecular work, a stock solution was prepared of various solutions, including DNA extraction and electrophoresis buffers. The following was the method of preparation of the solutions:

Tris HCl (1M, pH 8): Tris base (121.4 g) was dissolved in 500 ml of pure water. Concentrated HCl was added to the pH to bring it to the necessary level and the solution was distilled to 1000 ml with distilled water. The solution was put in autoclave and allowed to remain at room temperature.

EDTA (0.5M, pH 8.0): 300ml distilled water was put in EDTA (186.2 g). NaOH was put in to bring the pH to the right value and the final volume was adjusted to 1000 ml. The solution was maintained in autoclaved and room temperature.

NaCl (6M): 800 ml of distilled water was placed in NaCl (351 g). The volume was accommodated to 1000 ml of volume, autoclaved, and left at room temperature.

2.1.2 Work Strategy

2.2 Identification and Enrollment of Cataract-Affected Families

In this identification and screening of the impacted families of two or more individuals were used

to trigger the research. A write consent form was provided in the form of an informed participation form and a detailed form was provided to all the participants. The primary objective was to carry out a study on families and had the history of cataract and were willing to go through genetic tests.

2.2.1 Collection of Blood Sample

The subjects were sampled with blood and their parents as well as any siblings who were not affected. Five-ten ml of the venous blood was transferred to sterilized falcon tubes to every one of them with 0.25ml of 0.5M EDTA to prevent clotting. The blood samples stored at -70deg C were used to extract DNA and family pedigrees were drawn using Cyrillic software.

2.2.3 Laboratory Work

Once the blood samples collected, DNA extraction was performed according to the protocol, quantification made and exome sequencing was prepared. This was a research step involving a number of processes that resulted in purification and integrity of extracted DNA.

2.2.3 DNA Extraction

The extractive process was done using organic technique to obtain DNA of blood in order to isolate the genomic DNA of the white blood cell or the WBCs which are the only cells in blood, that have a nucleus on them. The measures were taken according to the following manner:

The samples of the blood were thawed, and was mixed with T.E. buffer so as to remove the red blood cells (RBCs). It was centrifuged at 5000 rpm over 25 minutes at 4degC and the resultant supernatant discarded and the WBCs were left in the pellet.

Pellet of WBC was washed a number of times and then further digested with the aid of TNE buffer, proteinase-K and SDS. The samples were incubated in 37degC.It was the second day on which the protein digestion was checked. Another proteinase-K treatment was done in the event of undigested material. The use of phenol- chloroform-isoamyl alcohol (PCI) and isopropanol precipitation of the DNA in use were used to separate the DNA.

The DNA was then ethanol treated and dried and stored in low TE buffer at 20 o C. Agarose Gel Electrophoresis was employed to measure the DNA by subjecting it to the stain procedure.

Agarose gel was used to identify the concentration of the DNA. The DNA samples were diluted and agarose gel was cast on the agarose gel that was stained using ethidium bromide and prepared in TBE buffer. The concentration of the DNA in the sample was calculated as the ratio of the fluorescence of the sample and a standard DNA marker.

2.2.4 Whole Exome Sequencing

Exome sequencing was done using the Twist Complete Exome panel and the HiSeq 4000 sequencing technology. The sequencing steps that were followed are as follows:

Library Preparation: To obtain the exonic regions of the genome, The Twist Complete Exome Panel was applied.

Sequencing: Hi-seq 4000 was carried out and the coverage rate of an average site of a nucleotide was 100-120X.

Data Processing: Raw data was aligned to the human genome reference sequence with the NoVo align tool. Quality control and recalibration of base quality was done using Haplotype Caller.

Variant Calling: GATK v.3.0 was employed to call variants which were mapped to homozygous.

Pathogenicity Assessment: THE AN-NOVAR and in-house scripts were used to evaluate the pathogenicity of the identified genomic variants based on the frequency data, obtained in Genome Aggregation Database (gnomAD) and on the estimates of the functional impacts.

2.2.5 Family Pedigrees

The family pedigrees of each family with cataract-affected individuals were drawn with all care in order to follow the pattern of the inheritance and the potential ties with the genetic. The following were the investigated families:

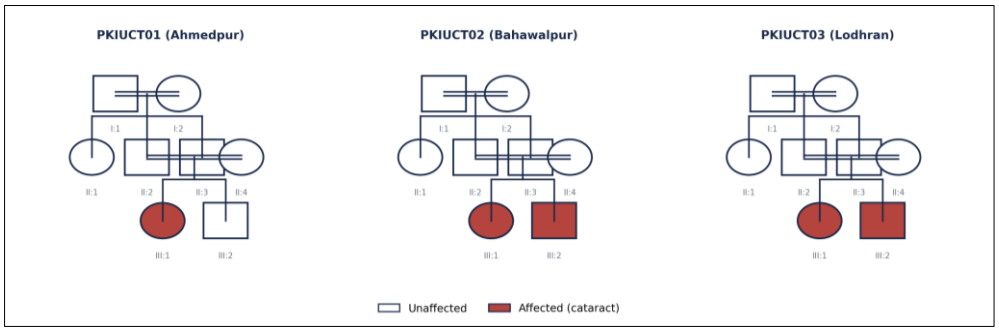


Figure 2.1: Schematic consanguineous pedigrees of the three enrolled Pakistani families (PKIUCT01, PKIUCT02, PKIUCT03), illustrating first-cousin unions and affected offspring

Family PKIUCT01: This was a family that had two affected individuals in it and the two were reported to be consanguinously married. Symptoms of cataract had started at an earlier age than when the study was carried out due to which the sampled were between their twenties.

Family PKIUCT02: This was a family that was based in Bahawalpur where the two affected family members began to exhibit their symptoms at a tender age. When he grew up, it gradually progressed and had an infection in both eyes.

Family PKIUCT03: Family was discovered in Lodhran and two affected male individuals in this family had progressive cataracts and had virtually no vision by the age of thirty years.

3. RESULTS

the findings from the mutational analysis of the FOXE3 gene in cataract-affected families from Southern Punjab, Pakistan. The analysis included clinical evaluation, DNA extraction, whole-exome sequencing (WES), and variant identification.

3.1 PKIUVI 133

This family was identified from the Ahmedpur. Total two members were affected with the cataract in this family (Fig 3.1). This family had consanguineous marriage. At the time of sampling the individuals, IV: 1 was 10 years old and individual, IV: 2 was 8 years old. All other family members were not affected with this disease.

The patients had because cataract disease because their lens was cloudy. They cannot visualize properly, especially at nighttime. At the time of birth this cloudiness was mild but gradually the cloudness increased and caused the decreased in vision. The other member IV:2 has the same issue, but their disease started at the age of 3 year

The DNA of individual IV:1 was sent to our research collaborators at the Institute of Ophthalmology, Basel, Switzerland for whole exome sequencing. During whole exome sequencing analyses a mutation; NM 012186.3 in exon 1 of FOXE3 gene at position 720 causing Cytosine to Adenine (c.720 C>A) was identified in a family PKIUVI133. This mutation results the stop codon for cysteine at codon 240 (C240X) and causes premature termination of foxe3 protein.

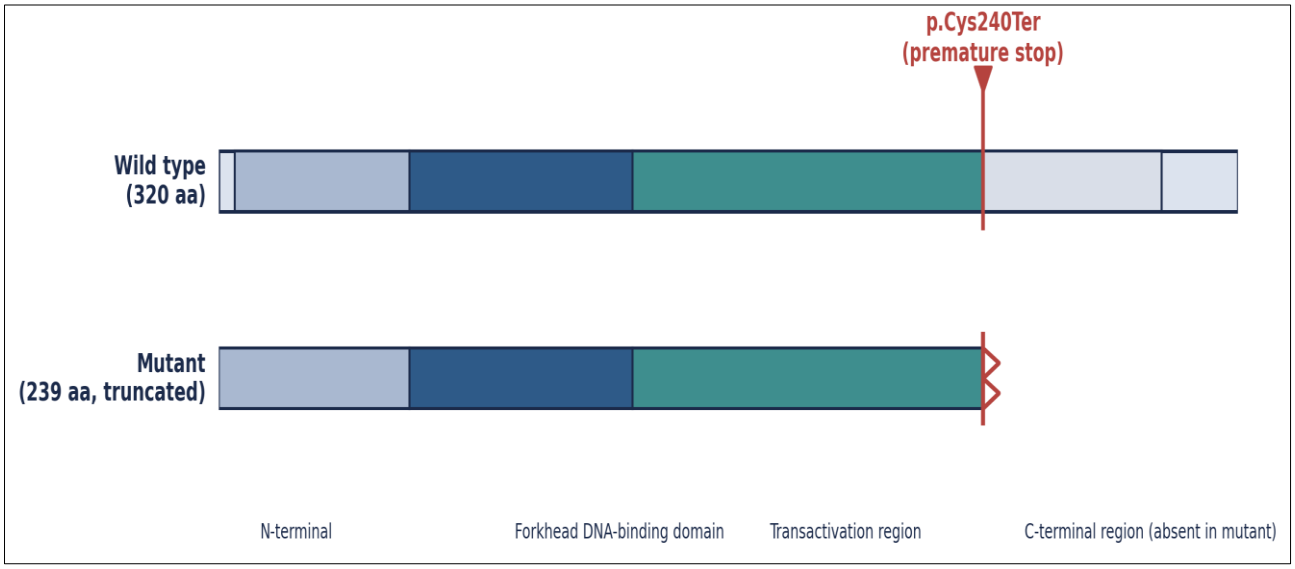


Figure 3.1: Schematic domain map of the FOXE3 protein showing the position of the c.720C>A (p.Cys240Ter) mutation relative to the forkhead DNA-binding domain and transactivation region

The FOXE3 gene was also sequenced by Sanger's sequencing method using DNA of affected and normal individuals of PKIUVI133 to confirm the mutation. Both the affected individuals were homozygous for the mutation and parents and some normal siblings were heterozygous for mutation. This confirmed the mutation

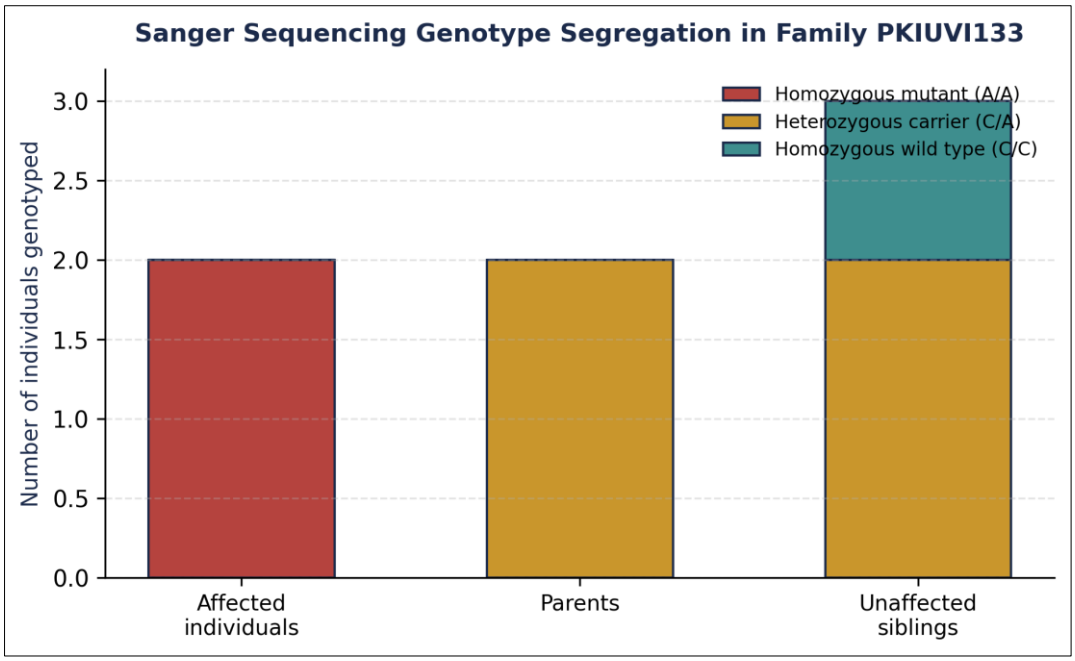


Figure 3.2: Sanger sequencing genotype segregation of the FOXE3 c.720C>A variant among affected individuals, parents, and unaffected siblings of family PKIUVI133

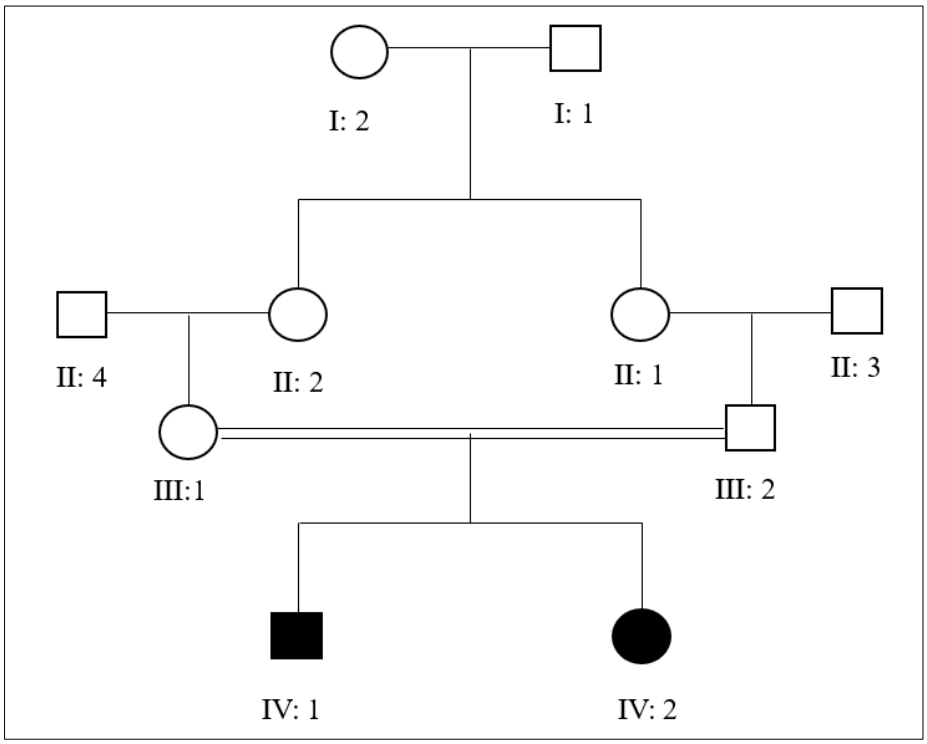


Figure 3.3: Pedigree of family PKIUVI 131.Square denote male, circle denote female, Blank Square /circle denotes normal person, black shades denote affected persons and double line denote cousin marriage

3.2 Comparison of Wild and muted sequence

Mutant sequence was put in Ensemble to verify the mutation. The mutated sequence was compared to wild type of FOXE3 gene.

481 GGCCGCAGACATGTTCGACAACGGCAGCTTCCTGCGGCGCCGCAAGCGCTTCAAGCGCGC 540
450 GGCCGCAGACATGTTCGACAACGGCAGCTTCCTGCGGCGCCGCAAGCGCTTCAAGCGCGC 509
150 --A--A--D--M--F--D--N--G--S--F--L--R--R--R--K--R--F--K--R--A 170

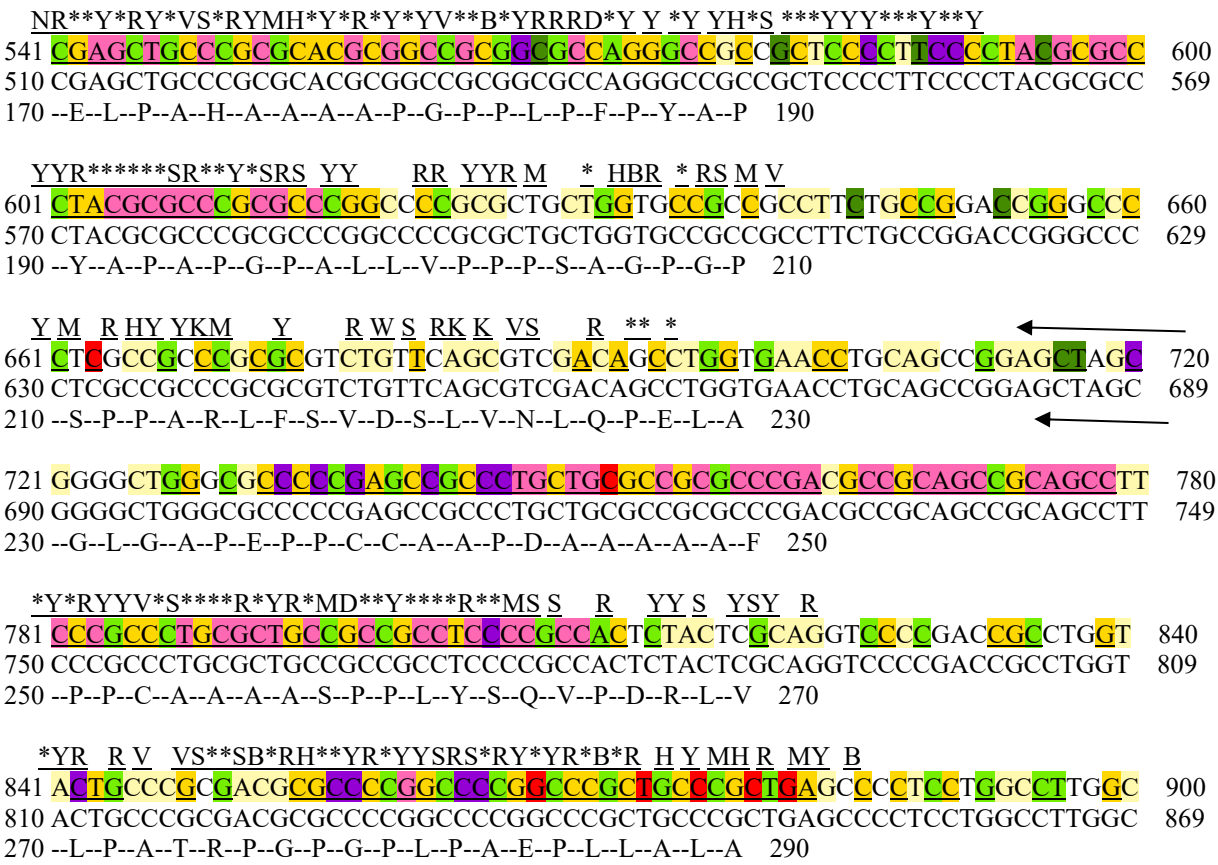


Figure 3.4: Showing the comparison of Normal FOXE3 gene sequence with reported mutation. For examining the conversion of nucleotide to amino acid nucleotide to amino acid translator software was used. That showed that mutation at the position of C.240 in the family PKIUVI133

Wild type

MTGRSDMEPPAAFSGFPAPPSVAPSGPPPSPLAGAEPGPEPAEAAAGRGEPEPAPAPGPG
RRRRRPLQRGKPPYSYIALIAMALAHAPGRRLTLAAIYRFITERFAFYRDSPRKWQNSIR
HNLTLNDCFVKVPREPGNPGKGNYWTLDPAAADMFDNGSFLRRRKRFKRAELPVLPAPPP
AAGPPPFPYAPYAPGPGPALLAPPPPAAPGSAPPARLFSVDSLVSLPPELAGLGAPEPPC
CAAPDAAFSPCTASPPLYSPPPDRLGLPATRPGPGPLPAEPLLALAGPGTALGPLGPGEA
YLRPPGYAPGLERYL

Figure 3.5: Showing normal sequence of amino acid resulted from FOXE3 gene

Mutated type

RRRRRPLQRGKPPYSYIALIAMALAHAPGRRLTLAAIYRFITERFAFYRDSPRKWQNSIR
HNLTLNDCFVKVPREPGNPGKGNYWTLDPAAADMFDNGSFLRRRKRFKRAELPVLPAPPP
AAGPPPFPYAPYAPGPGPALLAPPPPAAPGSAPPARLFSVDSLVSLPPELAGLGAPEPPX

Figure 3.6: Showing mutated sequence of amino acid resulted from FOXE3 gene mutation in PKIUVI133

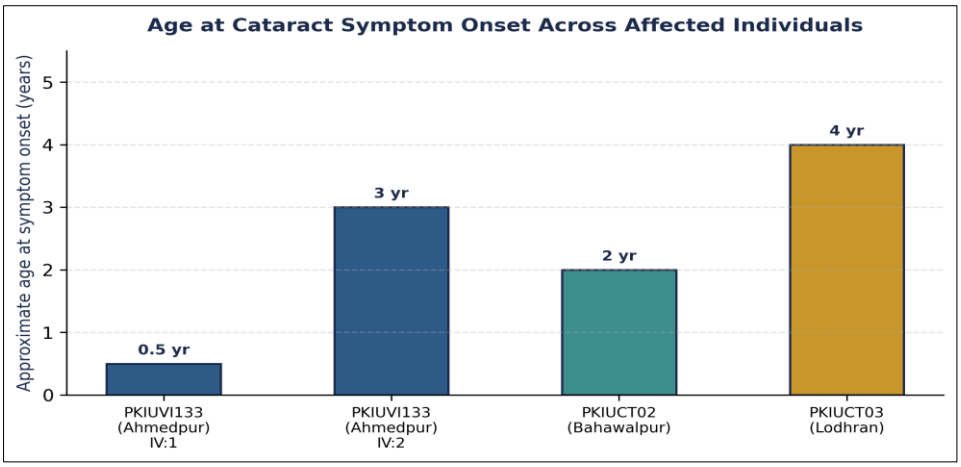


Figure 3.7: Approximate age at cataract symptom onset for the affected individuals across the studied families

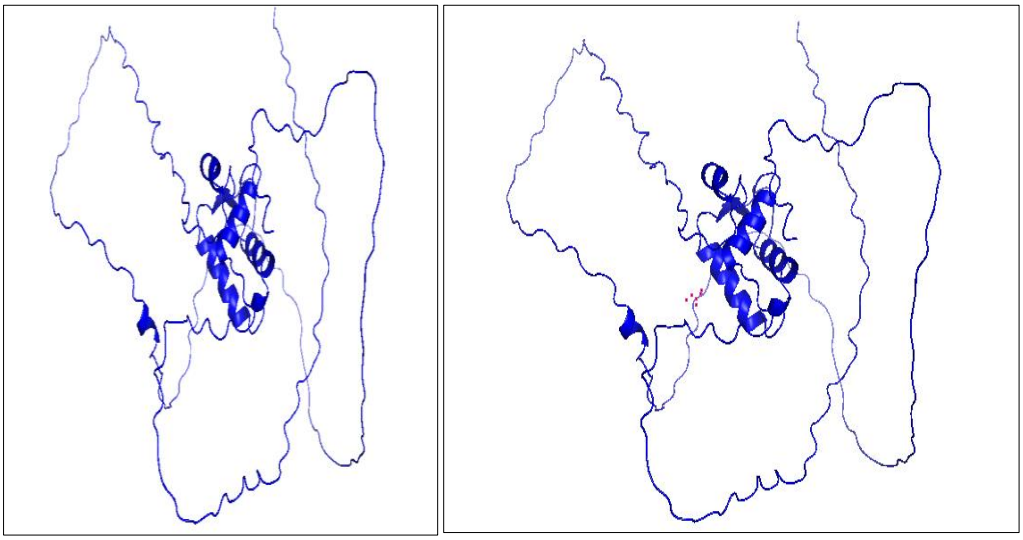


Figure 3.8: Mutated Protein Structure Sequenced from FOXE3

4. DISCUSSION

The case study findings have indicated that a mutation of the FOXE3 gene C720A is likely to be the cause of congenital cataracts in most of the Southern Punjab based families in Pakistan. The mutation leads to early stop codon occurrence at the 240 locations of FOXE3 protein (C240X), and results in the production of a truncated protein that is supposed to destabilize the normal development of the lens. This finding plays a significant part in the genetic etiology of cataracts particularly in consanguinity with genetic disorders dominating and exceedingly elevated.

The blindness caused by congenital cataracts in most parts of the globe is a significant cause of blindness and genetic factors in the pathogenesis of cataracts are rather essential. Genetic basis of congenital cataracts has been linked to mutations in a number of genes including FOXE3 even though the genetic basis of the condition is not well established in a number of population groups. Previous studies have discovered mutation in the FOXE3 gene that encode a transcriptional factor needed during normal development of the lens. It has been demonstrated that FOXE3 mutations cause a spectrum of eye diseases including the cataract in isolation as well as severe diseases such as anterior segment malformation and aphakia (Reis *et al.,* 2007; Semina *et al.,* 2001). We validate the current reports linking the mutations of FOXE3 to early cataracts.

The c.720C-A mutation observed in FOXE3 had been observed in all the possible cases of three families co-segregating with the cataract phenotype and thus had close genetic relationship. This mutation results in an early stop codon at position 240 which is likely to truncate FOXE3. FOXE3 is a transcription factor, which plays a role in the regulation of the lens-specific proteins, and a truncated protein is likely to disrupt the processes of regulation, leading to opacification of the lens (Shiels *et al.,* 2015). We observe that mutations of FOXE3 have already been truncated in other previous studies to create developmental cataracts (Baltussen *et al.,* 2017).

The clinical presentation identified in the individuals who were affected was in line with the prior accounts of FOXE3 mutations. In our case, the affected individuals had bilateral progressive cataracts that started to develop during childhood and the symptoms progressively worsened as they advanced in age. The intensity of the issue was varied, with certain patients being more influenced by the rapid growth of the transparency of the lens, which ultimately led to a severe visual impairment. This outcome is also consistent with the expressivity variant of the other FOXE3-related cataract cases in which the onset age and severity of the cataract can differ among members of a particular family (Anjum *et al.,* 2017).

Homologous or compound heterozygous mutation which is typical of recessive genetic diseases may have been transmitted because of high consanguinity of the family under study. In case of high consanguinity, the risks of inheriting rare and recessive mutations are greater, and, probably, that is why the levels of cataracts are high in the families that we studied (Rashid *et al.,* 2020).

Cataracts can be developed due to more genetic factors along with FOXE3 mutation. We were interested in the FOXE3 gene; however, whole exome sequencing did not reveal any other significant mutation in the cataract related genes of interest, and, therefore, FOXE3 may be the causative gene that is most prominent in these families. However, the impact of environmental factors cannot be ignored entirely and the study should be extended to cover the fact that the environmental risk factors might have some role to play in the process of cataract formation of the population.

CONCLUSION

This study applied an integrated genetics, molecular biology, biotechnology and bioinformatics approach to investigate inherited cataract in a consanguineous Pakistani family. Pedigree evaluation supported an autosomal-recessive inheritance pattern, while whole-exome sequencing and bioinformatics analysis identified the homozygous FOXE3 variant NM_012186.3.720C>A. Sanger sequencing confirmed the variant in both affected individuals and demonstrated heterozygous carrier status in their parents and some unaffected family members, supporting segregation of the variant with the ocular phenotype.

At the molecular level, the c.720C>A substitution introduces a premature termination codon, NP_036318.1. Cys240Ter, and predicts the formation of a shortened FOXE3 protein lacking its C-terminal region. Although this finding supports the involvement of FOXE3 in the phenotype observed in the family, the variant has been reported previously and no functional experiments were conducted in the present study. Therefore, the results should be interpreted as strong genetic and molecular segregation evidence rather than direct experimental proof of the pathogenic mechanism.

The study demonstrates the value of sequencing biotechnology combined with bioinformatics-based variant prioritization for diagnosing inherited ocular disorders in consanguineous populations. Molecular confirmation can support early diagnosis, carrier identification, family screening and informed genetic counseling. Future research should include detailed ophthalmic phenotyping, analysis of additional affected families and functional evaluation of the truncated FOXE3 protein to clarify the relationship between the variant and the observed clinical presentation.

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