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WHOLE EXOME SEQUENCING REVEALS THE GENETIC LANDSCAPE OF INHERITED OCULAR DYSTROPHIES IN CONSANGUINEOUS FAMILIES FROM NORTHWESTERN PAKISTAN

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Abstract

Inherited Ocular Dystrophies comprise a heterogeneous group of rare and complex diseases commonly caused by gene mutations, resulting in progressive degeneration of various structures within the eye including the retina, cornea, lens, and other parts. Approximately one in 1000 people worldwide have genetic eye diseases. This research aimed to investigate the genetic causes of inherited ocular diseases in families from District Haripur. Families with at least two individuals diagnosed with inherited ocular disorders (IODs) were identified and tested through the Shifa Eye Foundation. Saliva samples were collected from patients, their parents, and at least one healthy sibling to serve as a control. Genomic DNA was extracted from these saliva samples, and whole exome sequencing (WES) was performed on one individual per family. The WES data were then filtered using computational methods. A total of ten IOD families from various localities within District Haripur were studied, and consanguinity was observed in all these families. Pathogenic mutations were identified in six families, resulting in a diagnosis success rate of 60%. In total, 16 deleterious alleles across six different genes were found. Most of these mutations were non-synonymous, stop gain or frameshift, and most were homozygous. Due to the high rate of consanguinity in the region, this study indicates that homozygous harmful mutations predominantly characterize the genetic profile of IODs in District Haripur.

Keywords

Heterogeneous, Homozygous, frameshift, stop gain, non-synonymous, Whole Exome Sequence.

Article History

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INTRODUCTION

The human eye is a highly specialized sensory organ that captures visual information and converts light into neural signals for transmission to the brain. Vision primarily depends on the retina, a complex multilayered neural tissue composed of rod and cone photoreceptors that initiate the phototransduction cascade. Rod photoreceptors mediate scotopic (low-light) vision, whereas cone photoreceptors are responsible for photopic (daylight) vision, color discrimination, and high visual acuity (Dacey, 1996). Phototransduction begins with the photoisomerization of 11-cis-retinal to all-trans-retinal, activating rhodopsin and subsequently the transducin-mediated signaling pathway, which reduces intracellular cyclic guanosine monophosphate (cGMP) levels and induces photoreceptor hyperpolarization (Arshavsky et al., 2002). Regeneration of the visual chromophore

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through the retinal pigment epithelium (RPE) is essential for maintaining continuous visual function (Moiseyev et al., 2005). Disruption of any component of this highly regulated visual cycle by pathogenic genetic variants leads to progressive photoreceptor dysfunction and irreversible visual impairment.

Inherited ocular dystrophies (IODs) comprise a diverse group of rare monogenic disorders characterized by progressive degeneration of ocular tissues, including the retina, cornea, lens, optic nerve, and anterior segment structures (Nolen, et al., 2006). To date, more than 317 disease-causing genes and loci have been associated with these disorders, reflecting their remarkable genetic and phenotypic heterogeneity (Chan et al., 2023). IODs exhibit multiple inheritance patterns, including autosomal recessive, autosomal dominant, X-linked, mitochondrial, digenic, and oligogenic transmission, making accurate clinical diagnosis challenging (Ripollés-García et al., 2023). Clinically, these disorders are broadly categorized into inherited retinal dystrophies (IRDs) and inherited non-retinal ocular dystrophies.

Inherited retinal dystrophies are among the leading causes of inherited blindness worldwide, affecting approximately 1 in 2,000–4,000 individuals (Hanany et al., 2020). This heterogeneous group includes retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), cone and cone–rod dystrophies (CD/CRD), macular dystrophies (MD), choroideremia, Bardet Biedl syndrome (BBS), and Usher syndrome (USH). These disorders share common clinical manifestations such as night blindness, photophobia, progressive visual field constriction, impaired color vision, reduced visual acuity, and eventual blindness (Ellingford et al., 2016). Syndromic forms, including BBS and USH, are additionally associated with systemic abnormalities such as obesity, renal dysfunction, hearing impairment, developmental delay, polydactyly, and endocrine defects, reflecting the pleiotropic effects of mutations affecting ciliary and sensory signaling pathways (Fuster-García et al., 2021). In contrast, inherited non-retinal ocular dystrophies including congenital glaucoma, congenital cataract, corneal dystrophies, keratoconus, anophthalmia, and microphthalmia primarily affect anterior segment development or corneal integrity and represent important causes of childhood visual impairment (Li et al., 2024). The extraordinary genetic diversity and overlapping clinical phenotypes of inherited ocular dystrophies have limited the diagnostic accuracy of conventional clinical approaches. The advent of next generation sequencing (NGS), particularly whole-exome sequencing (WES), has revolutionized molecular diagnosis by enabling simultaneous analysis of all protein coding genes, substantially increasing diagnostic yield while facilitating the identification of novel disease-causing variants. Accurate molecular diagnosis is essential for establishing genotype phenotype correlations, improving genetic counseling, enabling carrier detection, supporting prenatal diagnosis, and identifying patients eligible for emerging gene and mutationnspecific therapies. Pakistan represents one of the world's most consanguineous populations, where autosomal recessive disorders occur at a disproportionately high frequency. Despite this, the molecular spectrum of inherited ocular dystrophies in Pakistani families remains incompletely characterized, and many pathogenic variants unique to this population are likely undiscovered. Therefore, this study employed whole-exome sequencing combined with comprehensive clinical phenotyping to investigate the genetic basis of inherited ocular dystrophies in consanguineous families from District Haripur, Pakistan. Identification of pathogenic variants and expansion of the mutation spectrum will improve molecular diagnosis, refine genotype–phenotype correlations, strengthen genetic counseling, and contribute to the development of precision ophthalmology for genetically underserved populations.

MATERIAL AND METHOD

3.1 STUDY AREA

This genetic study was conducted in Haripur district, a historic city located in the Hazara Division of Khyber Pakhtunkhwa province, Pakistan. It is situated in a hilly plain area, at an

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elevation of 520 meters (1,706 feet). According to the 2023 census, the district contains 192,451 households and has a population of 1,174,783 distributed across three tehsils: Haripur, Khanpur, and Ghazi. Haripur is situated in a hilly plain area, at an elevation of 520 meters (1,706 feet).

3.2 ETHICAL APPROVAL AND FAMILY RECRUITMENT

Ethical approval for this study will be taken from the departmental ethical consideration committee of The University of Haripur, KP Pakistan. Detailed Ophthalmic evaluations and fundus examinations were carried out at the Al Shifa Eye Foundation Haripur led to the diagnosis of Cone Rod-cone Dystrophy, Macular Dystrophy, Stargardt disease, Leber's Congenital Amaurosis, Bardet Biedl Syndrome, Retinitis Pigmentosa, Congenital glaucoma, congenital cataract, Keratoconus, and Microphthalmia/Anophthalmia Inclusion criteria will be based on at least two IOD patients per family. Affected and unaffected individuals of the family will be informed about the aims and objectives of the research in the local language. Signs of the participating individuals will be taking on the consent form to approve the publication of data and photographs.

3.3 QUESTIONNAIRE AND PEDIGREE CONSTRUCTION

The questionnaire will contain all the patient's demographic, clinical, ocular, and Non-ocular symptoms. Face-to-face interviews were conducted with patients and their family members in the local language to obtain information regarding family and medical histories. Based on the gathered information, pedigrees were constructed immediately after the interviews. The Pedigree Chart Designer tool (CeGat, Germany) was then utilized to create electronic pedigrees. In the diagrams, males were represented by squares and females by circles; unfilled symbols indicated unaffected individuals, while filled symbols represented those with the condition. Crossed squares and circles denoted deceased individuals, double lines between partners signified cousin marriages and Roman numerals indicated the different generations within a family.

3.4 SAMPLE COLLECTION

A total of 15 families will be enrolled in the study. Samples were collected from all the affected individuals and their parents (in the case of deceased parents, siblings will be included), and a sample from one healthy sibling will also be included. Saliva samples were collected from each participant using a disposable sampler saliva collection kit with ITM (Wu-xi NEST Biotechnology Co., Ltd, China, and NEST Scientific Inc, USA). Each kit includes a 10 ml vial with a funnel and a 5 ml vial containing 2.0 ml of sterile ITM. It is essential to follow the manufacturer's instructions for using these vials.

3.5 DNA EXTRACTION

DNA was extracted from the collected samples robotically following the protocols outlined by Thermo Fisher Scientific's MagMAX™ Saliva gDNA Isolation Kit. A Thermo Fisher Scientific NanoDrop™ 1000 spectrophotometer and 1% agarose gel electrophoresis were employed to evaluate the DNA quality and quantity.

3.6 WHOLE EXOME SEQUENCING (WES)

This technique includes sequencing the genome's protein-coding region, a commonly used next-generation sequencing (NGS) strategy. Retinal gene–targeted NGS was performed in Switzerland based on samples. A 100 ng/µl of genomic DNA is needed for full Exome sequencing. WES DNA was subjected to one of the abnormal individuals from each IOD's family. An Exome analysis containing approximately 20000 exomes was performed to identify the variant of interest.

3.7 DATA ANALYSIS

The different types of online bioinformatics tools were used to confirm the variant's Pathogenicity including Mutation Tester (http://www.mutationtaster.org), Polyphene 2 (http://genetics.bwh.harvard.edu/pph2/), Variant validator (https://www.https://variantvalidator.org/), VarSome (http://varsome.com), Orphanet

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(https://www.orpha.net), and OMIM (https://www.omim.org).

RESULTS

4.5.1 Demographic, Medical, and Genetic Details of Family ZA01

Family ZA01, from District Haripur, includes four children and is characterized by consanguineous parents. The family features two affected males, two unaffected females, and healthy parents. The Shifa Eye Foundation diagnosed inherited ocular disease (IOD) in the affected children. Common issues reported among participants with IODs included blurred vision, daytime vision difficulties, poor coordination, muteness, deafness, polydactyly, obesity, and anemia. In family ZA01, a homozygous stop gain (verified by varsome, intervar) ten nucleotide variant (NM_001348042:exon2:c.128C>A:p.S43X|BBS9:NM_001033604:exon3:.263C>A:p.S88X|BBS9:NM_001033605:exon3:c.263C>A:p.S88X|BBS9:NM_01348036:exon3:c.263C>A:p.S88X|BBS9:NM_001348040:exon3:c.263C>A:p.S88X|BBS9:NM_001348041:exon3:c.263C>A:p.S88X|BBS9:NM_001348043:exon3:c.263C>A:p.S88X|BBS9:NM_001362679:exon3:c.263C>A:p.S88X|BBS9:NM_014451:exon3:c.263C>A:p.S88X|BBS9:NM_198428:exon3:c.263C>A:p.S88X) were identified in BBS9 (NP_001334971.1, NP_001028776.1) gene with cytogenetic location 7p14.3 (Variant validator, OMIM). The identified variant was pathogenic (varsome) following the autosomal recessive inheritance pattern (omim, Orphanet).

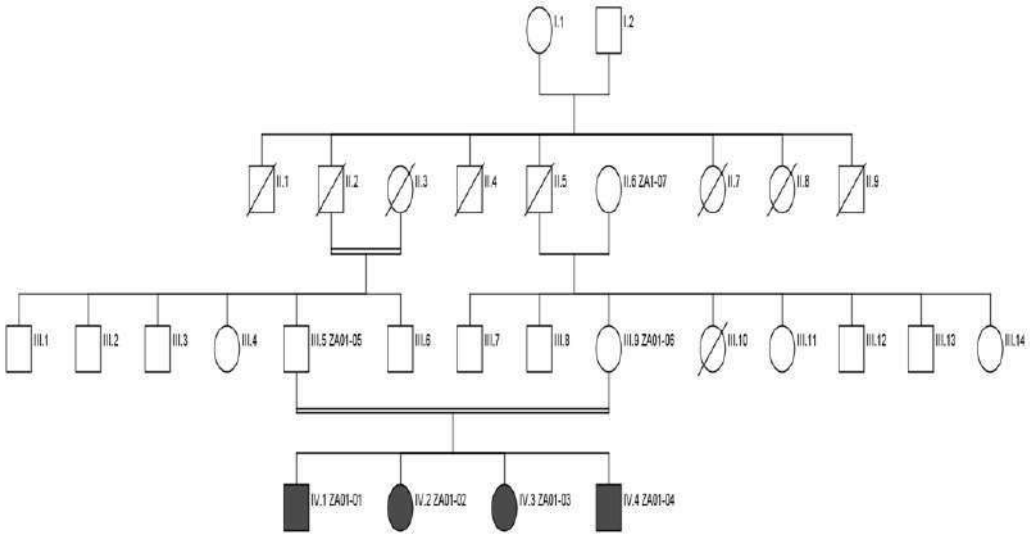

Figure 7.1 The Pedigree of FamilyZA01 reveals the consanguinity of their parents and the impacted family members

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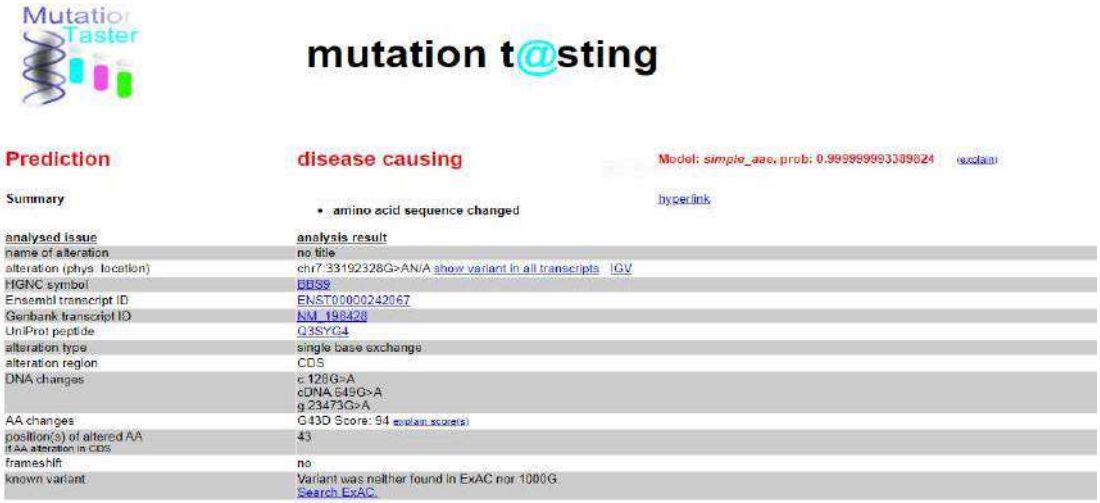

Figure 7.2 The Mutation Tester result, shows a score of 0.9999 which means disease-causing. It causes a pathogenic mutation for a known disease Bardet-Biedl Syndrome

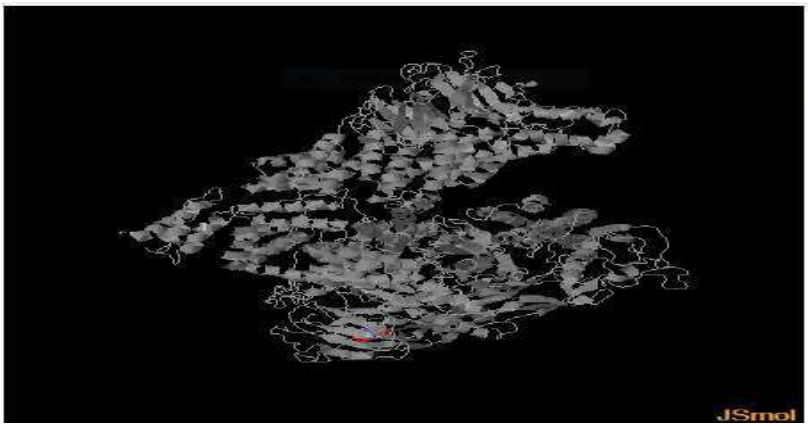

Figure 7.3 The Polyphen-2 reports for Q3SYG4 S88Q and this pathogenic mutation is predicted to be probably damaging with a score of 1.00 (sensitivity 0.00; specificity 1.00), with 3d visualization of this variant along with the pathogenic location (red color).

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4.5.2 Demographic, Medical, and Genetic Details of Family ZA03

Family ZA03, from District Haripur, includes six children born to consanguineous parents. The family has healthy parents and two daughters affected by the condition. The most obvious symptoms of affected patients were underdevelopment or absence of both eyes. In family ZA03, a homozygous frameshift deletion (verified by varsome, intervar) single nucleotide variant (NM_182894:exon4:c.679C>T: p.R227W) was identified in VSX2 (NP_878314.1) gene with cytogenetic location 14q24.3 (Variant validator, OMIM). The identified variant was pathogenic (varsome) following the autosomal recessive inheritance pattern (omim, orphanet). The gene VSX2 causing the microphthalmia was verified genetically

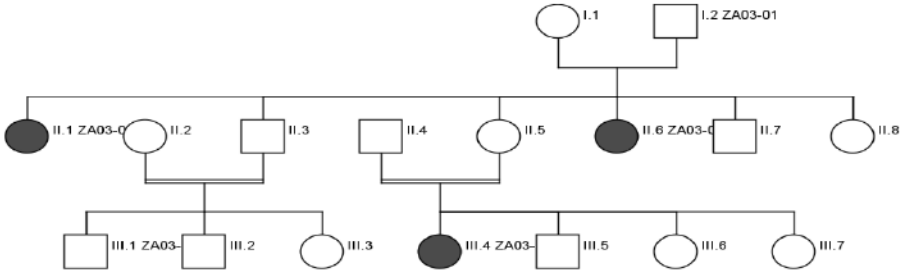

Figure 8.1 The Pedigree of FamilyZA03 reveals the consanguinity of their parents and the impacted family members.

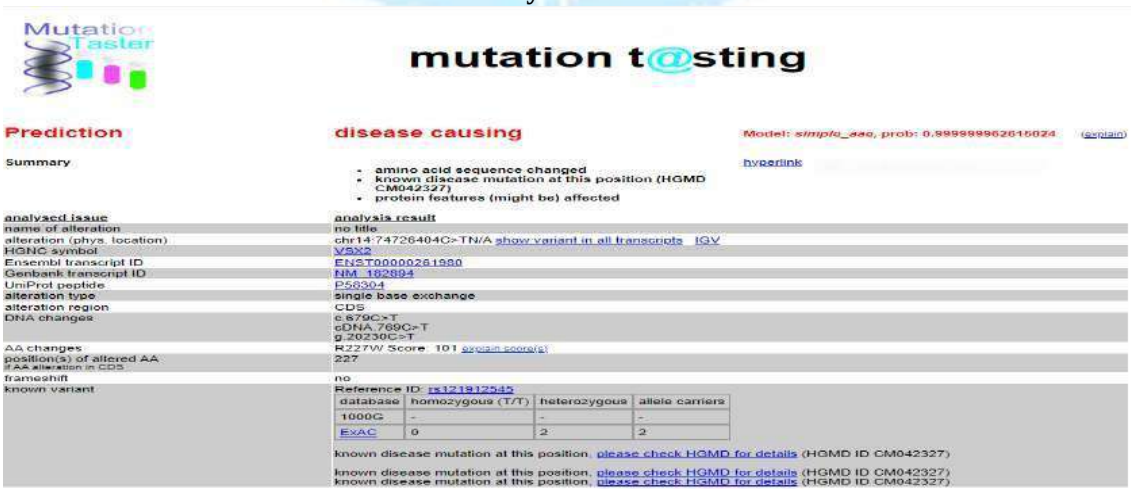

Figure 8.2 The Mutation Tester result shows a score of 0.9999 which means disease-causing. It causes a pathogenic mutation for a known disease Microphthalmia.

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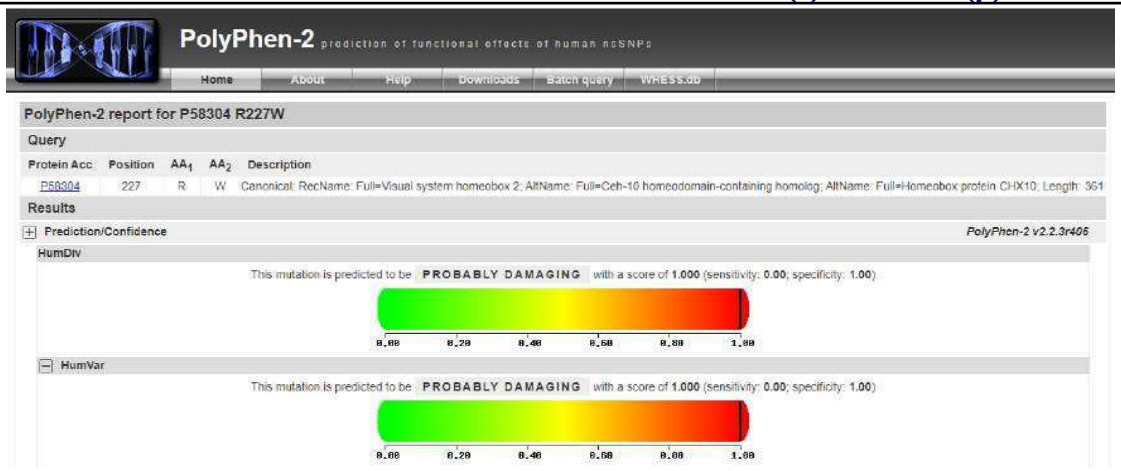

Figure 8.3 The Polyphen-2 reports for P58304 R227W and this pathogenic mutation is predicted to be probably damaging with a score of 1.00 (sensitivity 0.00; specificity 1.00).

4.5.3 Demographic, Medical, and Genetic Details of Family ZA04

Family ZA04, from District Haripur, includes four children of consanguineous parents. The family has healthy parents and two sons who are affected by the condition. The most prominent symptoms observed in the affected individuals were peripheral vision loss, central vision loss, night blindness, and color blindness. In family ZA04, a homozygous nonsynonymous SNV (verified by varsome, intervar) single nucleotide variant (RPGRIP1:NM_020366:exon16:c.2480G>T: p.R827L) was identified in RPGRIP1 (NP_065099.2) gene with cytogenetic location 14q11.2 (Variant validator, OMIM). The identified variant was pathogenic (varsome) following the autosomal recessive inhertance pattern (omim, orphanet) .The gene RPGRIP1 causing the CRD was verified genetically. An inheritance pattern of Autosomal recessive was demonstrated by pedigree-based research. A homozygous nonsynonymous mutation (NM_020366:exon16:c.2480G>T: p.R827L) was identified in the RPGRIP1 gene. In silico analysis of the variant was performed using online tools such as variant validator, Mutation Tester, etc.

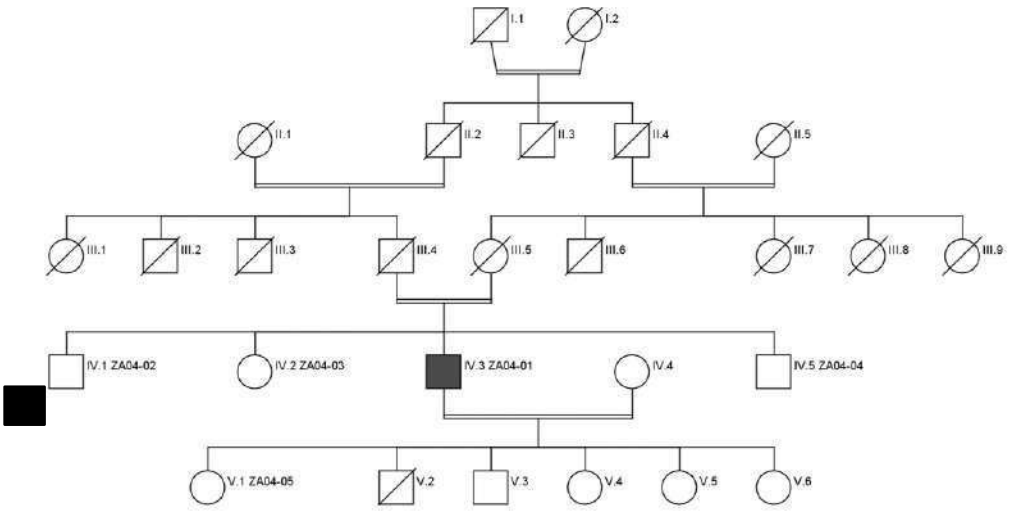

Figure 9.1 The Pedigree of FamilyZA04 reveals the consanguinity of their parents and the impacted family members.

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Figure 9.2 The Mutation Tester result shows a score of 0.9999 which means disease-causing. It causes a pathogenic mutation for a known disease CRDs.

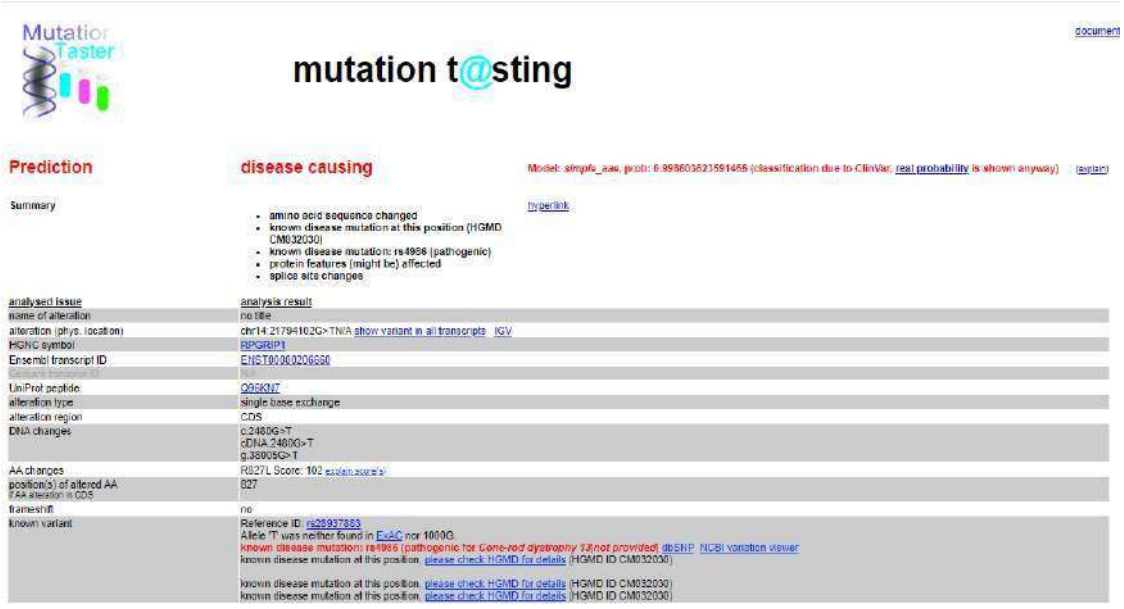

Figure 9.3 The Polyphen-2 reports for Q96KN7 R827L and this pathogenic mutation is predicted to be probably damaging with a score of 0.992 (sensitivity 0.70; specificity 0.97).

4.5.4 Demographic, Medical, and Genetic Details of Family ZA07

Family ZA07, from District Haripur, includes eight children born to consanguineous parents. The family has healthy parents and two affected children—one male and one female. The primary symptoms in the affected individuals were blurred vision, peripheral and central vision loss, night blindness, nystagmus, and strabismus. In family ZA07, a homozygous frameshift deletion (verified by varsome, intervar) double nucleotide variant (NM_001122769:exon7:c.1151_1152delinsA|LCA5:NM_181714:exon8:c.1151_1152delinsA) were identified in LCA5 NP_001116241.1, NP_859065.2) gene with cytogenetic location 6q14.1 (Variant validator, OMIM). The identified

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variant was pathogenic (varsome) following the autosomal recessive inhertance pattern (omim, orphanet) .The gene LCA5 causing the LCA was verified genetically.

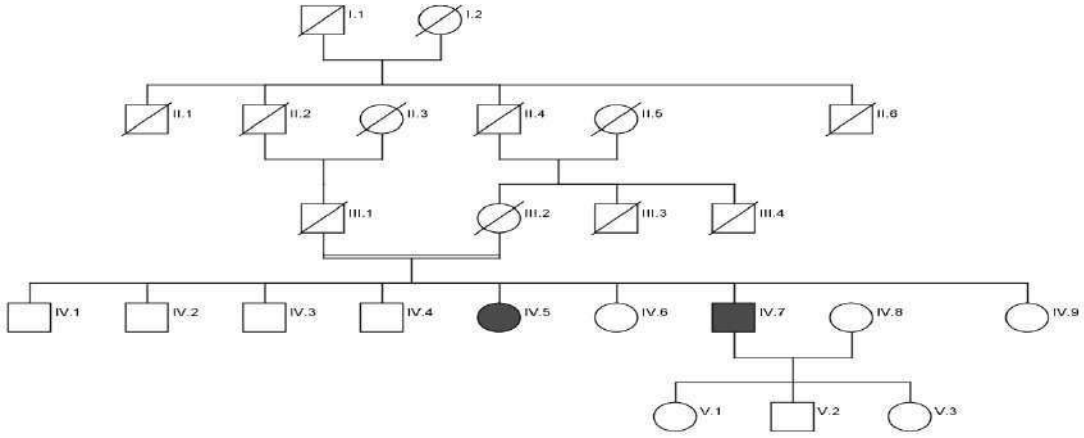

Figure 10.1 The Pedigree of FamilyZA07 reveals the consanguinity of their parents and the impacted family members.

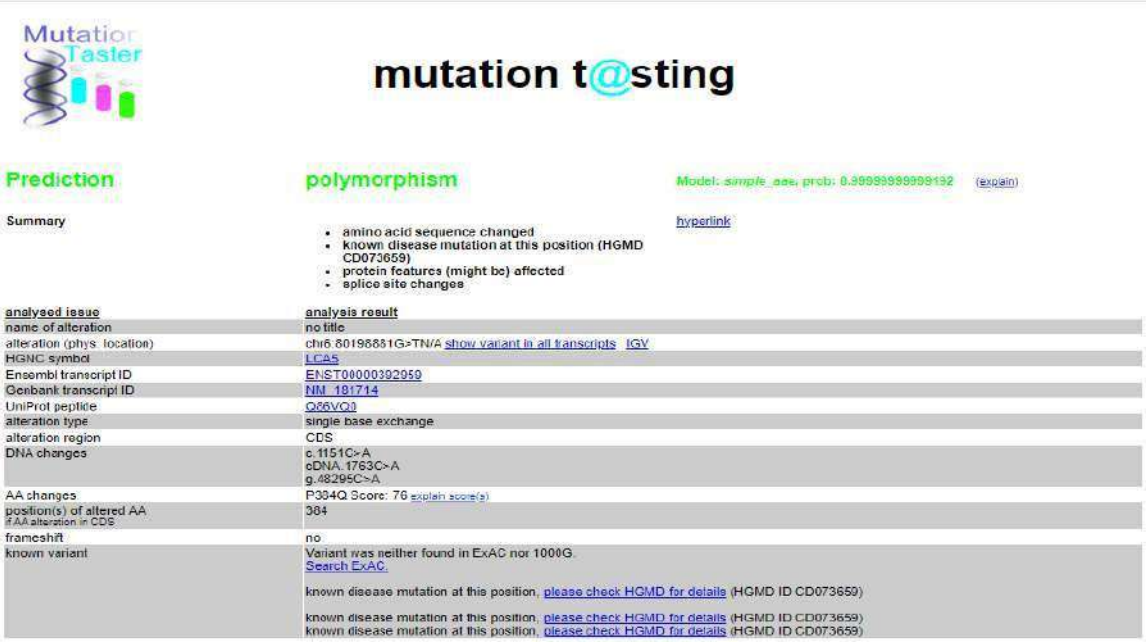

Figure 10.2 The Mutation Tester result shows a score of 0.9999 which shows polymorphism. It causes a polymorphic mutation for a known disease LCA.

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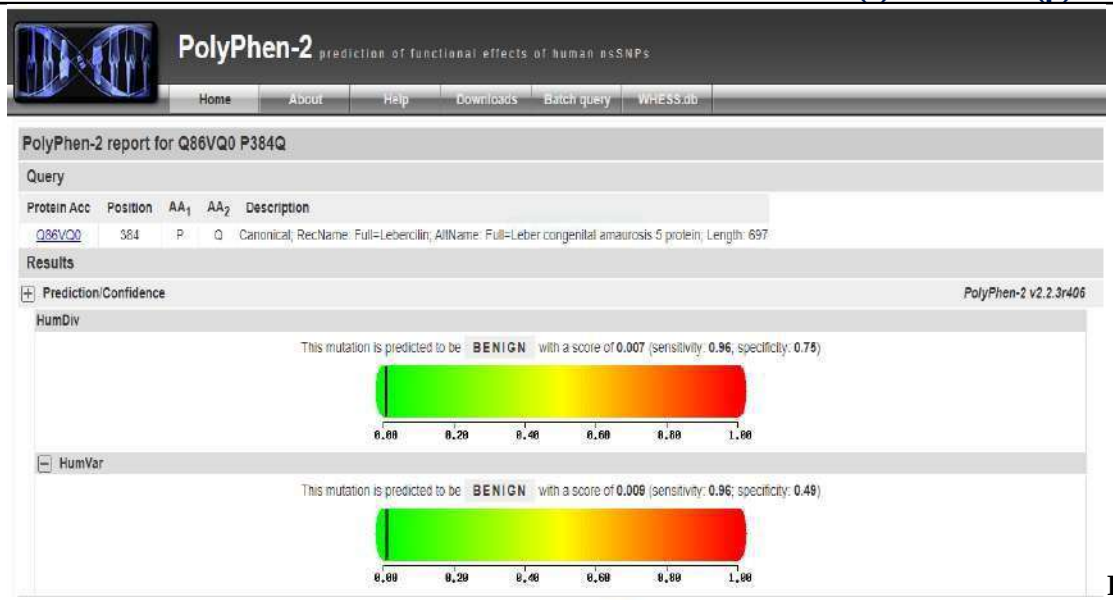

Figure 10.3 The Polyphen-2 reports for Q86VQ0 P384Q and this mutation is predicted to be Benign with a score of 0.007 (sensitivity 0.96; specificity 0.75).

4.5.5 Demographic, Medical, and Genetic Details of Family ZA08

Family ZA08, from District Haripur, consists of two affected individuals whose parents are consanguineous. Both patients are first cousins. The most obvious symptoms of affected patients were underdevelopment or absence of both eyes. In family ZA08, a homozygous nonsynonymous SNV (verified by varsome, intervar) single nucleotide variant (NM_000693:exon6:c.588C>G: p.C196W) was identified ALDH1A3 (NP_000684.2) gene with cytogenetic location 15q26.3 (Variant validator, OMIM). The identified variant was pathogenic (varsome) following the autosomal recessive inheritance pattern (omim, orphanet). The gene ALDH1A3 causing the anophthalmia was verified genetically.

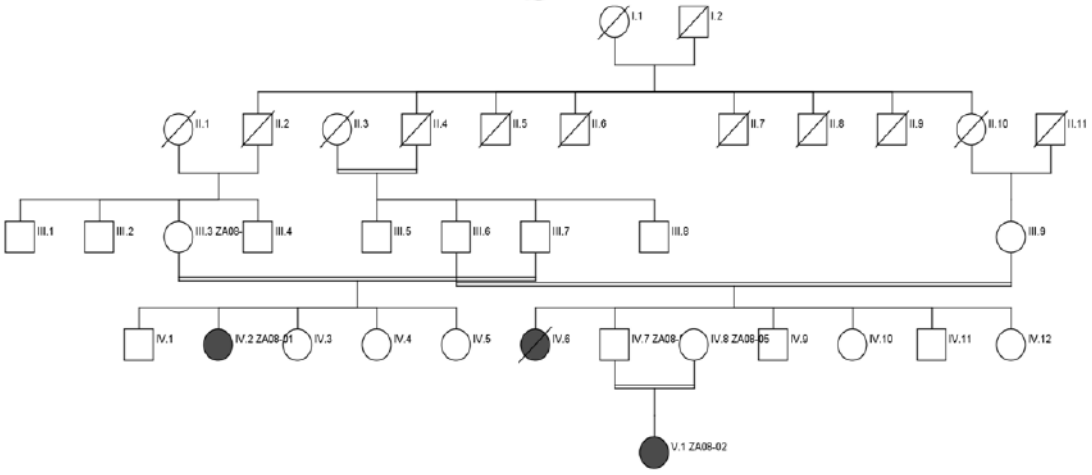

Figure 11.1 The Pedigree of FamilyZA08 reveals the consanguinity of their parents and the impacted family members.

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Figure 11.2 The Mutation Tester result shows a score of 0.9999 which means disease-causing. It causes a pathogenic mutation for a known disease Anophthalmia.

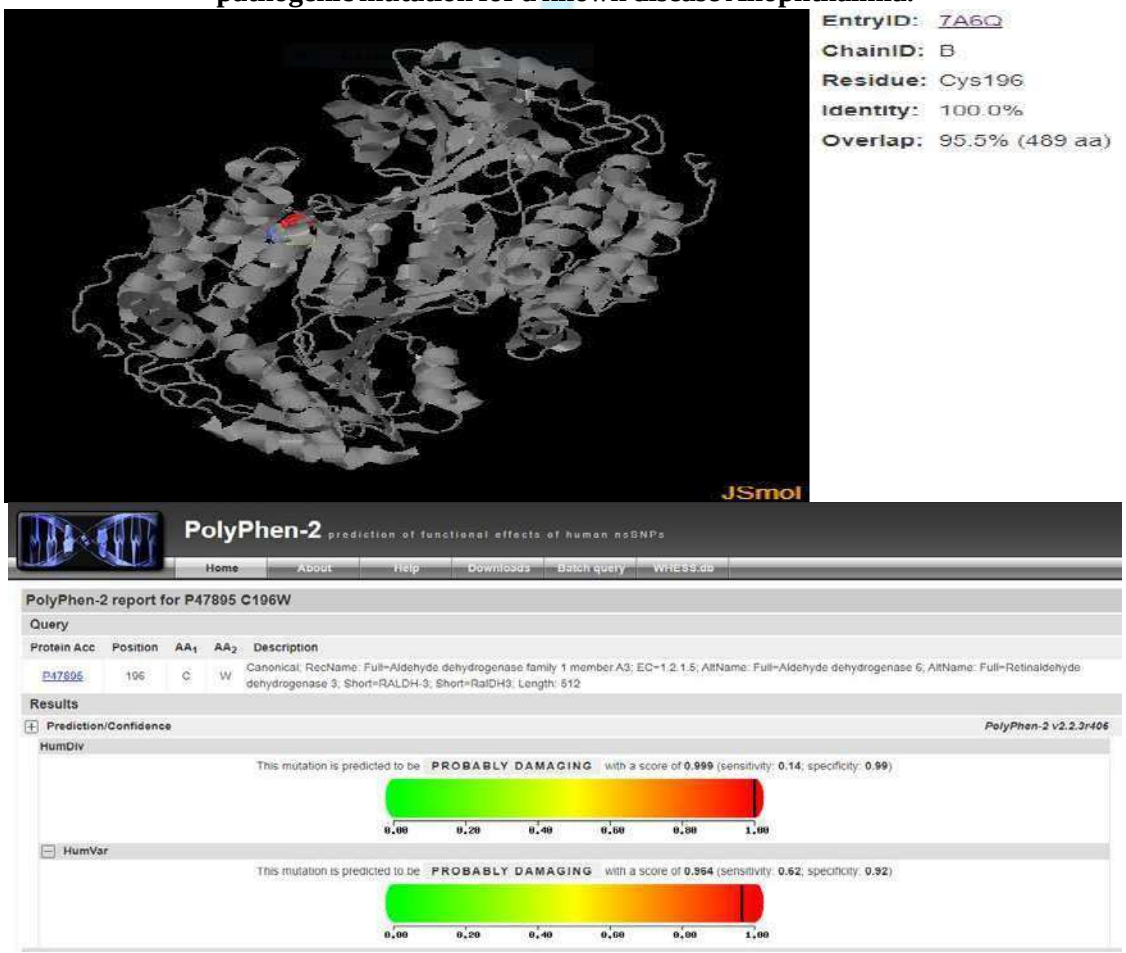

Figure 11.3 The Polyphen-2 reports for P47895 C196W and this pathogenic mutation is predicted to be probably damaging with a score of 0.999 (sensitivity 0.14; specificity 0.99).

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4.5.6 Demographic, Medical, and Genetic Details of Family ZA09

Family ZA09, from District Haripur, includes five children born to consanguineous parents. The family has healthy parents, two affected males, two affected females, and one affected female was expired. Participant's main queries, comprised Blurred Vision, Day vision problems, night blindness, Muteness, Deafness, intellectual disability, and growth delay. In family ZA09, a homozygous nonsynonymous SNV (verified by varsome, intervar) single nucleotide variant (NM_000180:exon18:c.3164G>C: p.W1055S) was identified as GUCY2D (NP_000171.1) gene with cytogenetic location 17p13.1 (Variant validator, OMIM). The identified variant was pathogenic (varsome) following the autosomal dominant inheritance pattern (omim, orphanet). The gene GUCY2D causing corneal dystrophy was verified genetically.

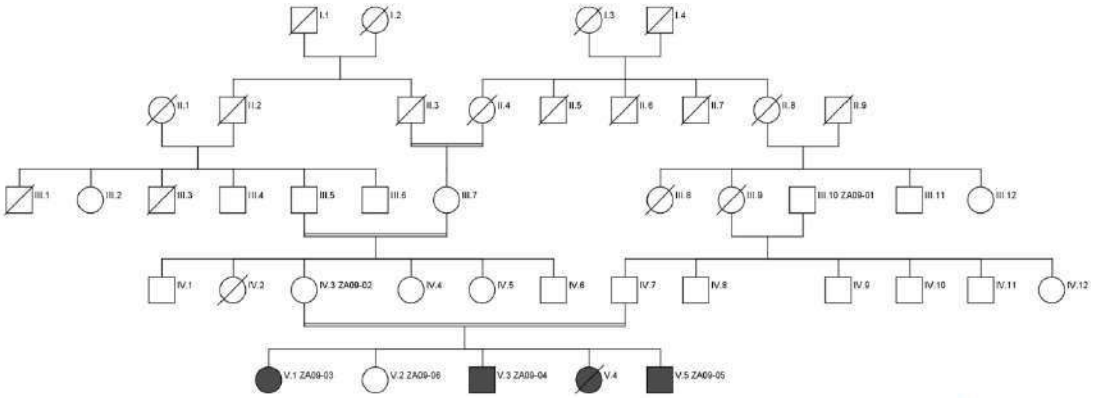
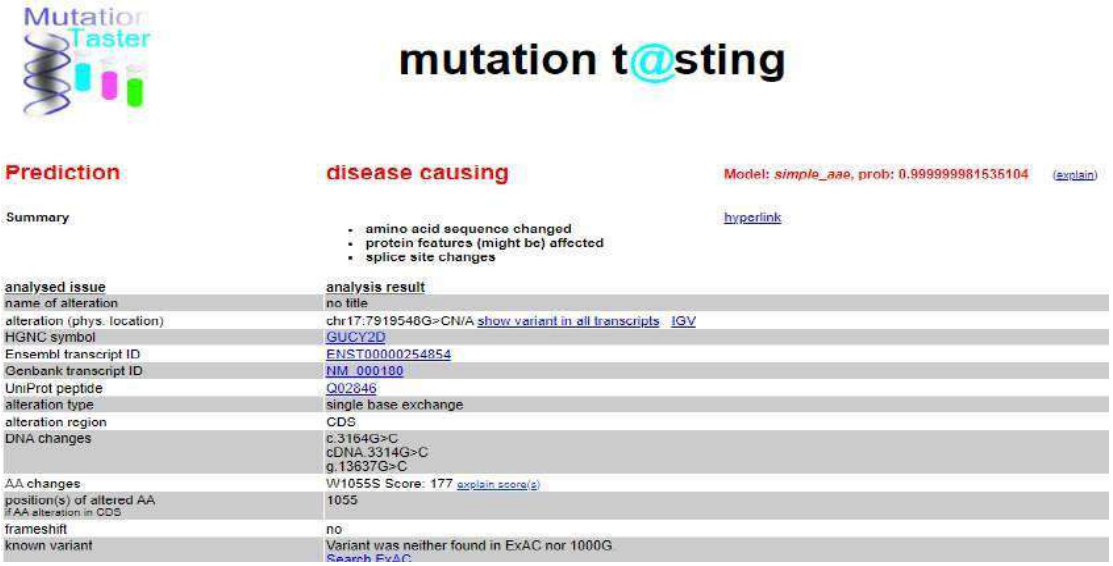


Figure 12.1 Pedigree of FamilyZA09 reveals the consanguinity of their parents and the impacted family members.



mutation t@sting

Prediction disease causing — Model: *simple_aae*, prob: 0.999999981535104 (explain)

Summary — hyperlink

- amino acid sequence changed
- protein features (might be) affected
- splice site changes

analysed issue	analysis result
name of alteration	no title
alteration (phys. location)	chr17:7919548G>CN/A show variant in all transcripts IGV
HGNC symbol	GUCY2D
Ensembl transcript ID	ENST00000254854
Genbank transcript ID	NM_000180
UniProt peptide	Q02846
alteration type	single base exchange
alteration region	CDS
DNA changes	c.3164G>C cDNA.3314G>C g.13637G>C
AA changes	W1055S Score: 177 explain score(s)
position(s) of altered AA if AA alteration in CDS	1055
frameshift	no
known variant	Variant was neither found in ExAC nor 1000G Search ExAC

Figure 12.2 The Mutation Tester result shows a score of 0.9999 which means disease-causing. It causes a pathogenic mutation for known disease CDs.

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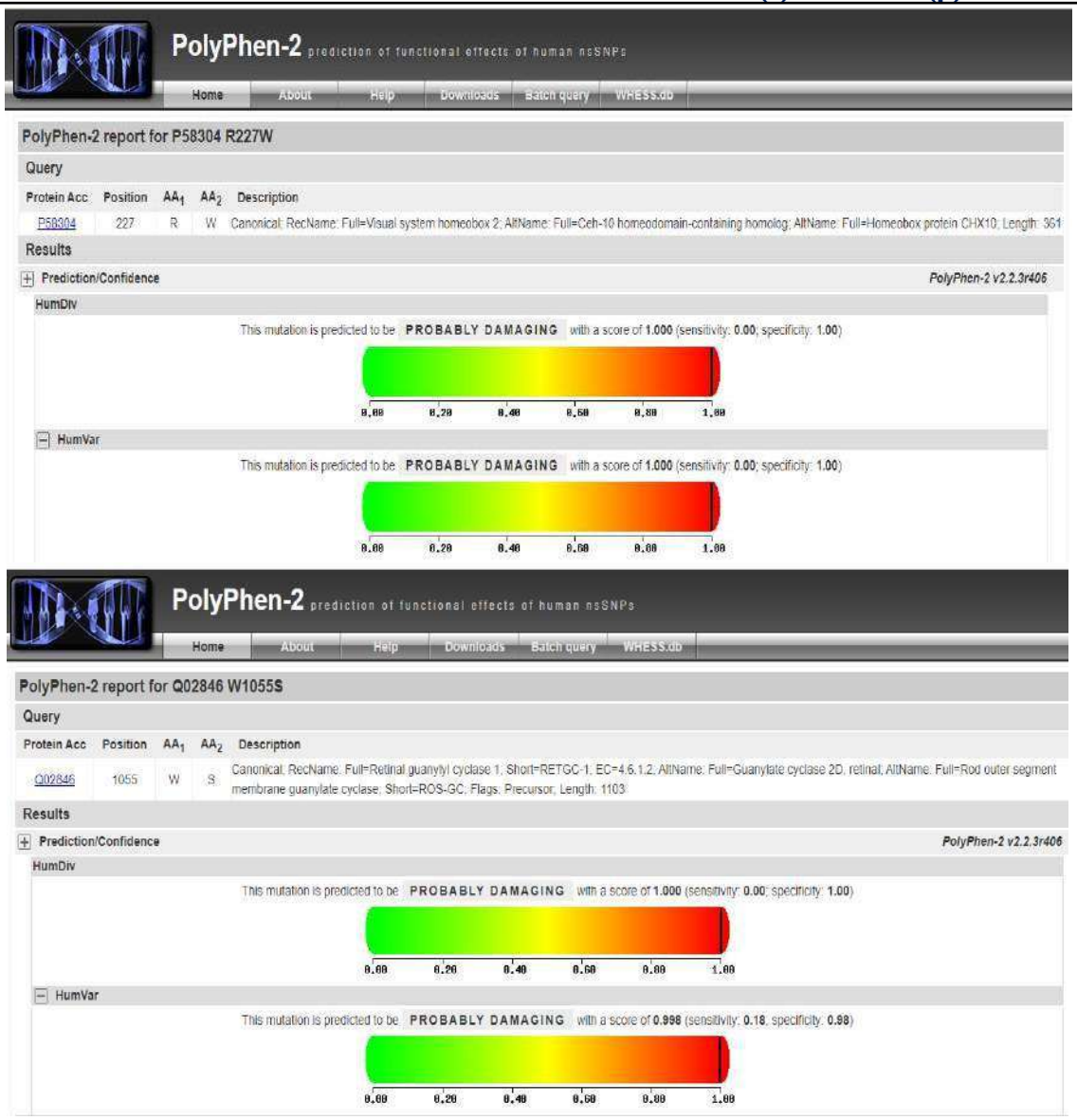

Figure 12.3 The Polyphen-2 reports for Q02846 W1055S and this pathogenic mutation is predicted to be probably damaging with a score of 1.00 (sensitivity 0.00; specificity 1.00).

DISCUSSION

This study represents the first molecular characterization of inherited ocular diseases (IODs) in families from District Haripur, Pakistan. Notably, the region exhibits one of the highest rates of consanguinity globally, with approximately 60% of marriages being consanguineous. Our investigation into ten families with IODs revealed a complete correlation between consanguinity and the occurrence of pathogenic mutations, as all identified mutations were homozygous. This finding starkly illustrates the influence of consanguinity on the genetic expression of rare Mendelian traits, as homozygosity is a direct consequence of this marriage pattern.

The study's results indicate that around 83% of the deleterious variants associated with IODs were inherited in an autosomal recessive manner. In contrast, 17% of variants followed an autosomal dominant inheritance pattern. These results emphasize the high prevalence of autosomal recessive inheritance within this population, aligning with the broader observation that approximately 97% of IOD mutations are typically

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autosomal recessive. This strong autosomal recessive component underscores the profound impact of consanguinity in shaping the genetic landscape of inherited ocular diseases in District Haripur.

IODs encompass a broad spectrum of over 60 distinct clinical forms globally, including conditions such as RP, LCA, MD, STGD, BBS, USH, choroideremia, CRD, anophthalmia, microphthalmia, CDs, CC, and CG. Our study identified a diverse array of IOD clinical types across the examined families, reflecting the rich clinical heterogeneity within the cohort. This diversity highlights the complexity of IODs and the need for comprehensive diagnostic approaches to address the varying manifestations of these diseases.

Molecular analysis led to the identification of pathogenic variants in six distinct genes associated with IODs among the families from District Haripur. The sequencing results demonstrated a range of mutations across these genes, further supporting the genetic diversity observed in this study. Specifically, pathogenic variants were detected in 6 out of the 10 families, yielding an overall diagnostic rate of 60%. This diagnostic yield is significant as it not only aids in understanding the genetic basis of the diseases but also informs disease prognosis and the development of targeted treatment strategies.

The identification of these genetic variants underscores the pressing need for genetic counseling and mutation screening in populations at risk for inherited retinal diseases and other genetic conditions. As genetic disorders continue to spread within the community, proactive measures, including genetic testing and counseling, are essential to manage and potentially mitigate the impact of these diseases. The insights gained from this study are crucial for advancing personalized medicine approaches and enhancing the quality of care for individuals affected by inherited ocular diseases in District Haripur and similar regions.

CONCLUSION

In conclusion, nearly all the families in our study were consanguineous. Inheritance patterns observed were predominantly autosomal recessive (83%), with autosomal dominant patterns accounting for 17%. Whole exome sequencing yielded a diagnostic success rate of 60%, revealing a total of 16 pathogenic variations. All identified alleles were homozygous. The variations included 23% stop gain, 32% frameshift, and 45% non-synonymous mutations.

RECOMMENDATIONS:

To gain a thorough understanding of the mutational frequency of inherited ocular diseases (IODs) and to identify region-specific variants, we recommend enrolling additional families from District Haripur.

To stop the spread of these conditions in the region, it is crucial to provide genetic counseling and carrier testing for affected families.

Additionally, we suggest organizing public seminars, workshops, or conferences to raise awareness and educate the local population about monogenic disorders.

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