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Molecular Characterization of Oculocutaneous Albinism in Pakhtun Families Reveals Recurrent Variants in *TYR* and *OCA2*

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ABSTRACT

Background: Oculocutaneous albinism (OCA) is a rare, genetically heterogeneous disorder characterized by impaired melanin biosynthesis and distribution in the skin, hair, and eyes. The severity of dermatological and ophthalmological manifestations varies depending on the underlying genetic defect. **Methods:** Five unrelated consanguineous families with multiple individuals affected by OCA were recruited from Khyber Pakhtunkhwa, Pakistan. Whole-exome sequencing (WES) was performed for the probands, followed by Sanger sequencing to confirm variant segregation. Variants were prioritized using the in-house VARDIGS pipeline and evaluated through population databases (gnomAD, ClinVar, HGMD), computational prediction tools (SIFT, PolyPhen-2, CADD, MutationTaster), and interpretation platforms (Franklin, VarSome, GeneBe). Final classification was performed according to ACMG guidelines. **Results:** Clinical evaluation revealed hypopigmented skin and hair, translucent irides, nystagmus, photophobia, and reduced visual acuity in affected individuals. Molecular analysis identified four recurrent pathogenic and one likely pathogenic variants in TYR and OCA2. Three variants were detected in TYR, including a frameshift variant c.216delA (p.Val74TrpfsTer46), observed for the first time in Pakistani patients, a missense variant c.132T>A (p.Ser44Arg), and a nonsense variant c.346C>T (p.Arg116Ter). Two variants in OCA2 including a missense variant c.1211C>T (p.Thr404Met) and a frameshift splice region variant c.2430delC (p.Phe810LeufsTer7) were identified in OCA2. Sanger sequencing confirmed co-segregation of all variants with the disease phenotype in respective families. In silico analyses consistently supported their pathogenicity with the exception of last OCA2 variant. **Conclusion:** This study reports five previously described variants, including three pathogenic in TYR, one pathogenic and one likely pathogenic OCA2 variants in consanguineous families of Pakhtun ethnicity, thereby expanding the mutational spectrum of OCA in the Pakistani population. The recurrence of these variants underscores the significant contribution of TYR and OCA2 to OCA in this region and highlights the impact of consanguinity. These findings have important implications for genetic counseling, carrier screening, and informed family planning.

INTRODUCTION

Albinism is a rare inherited genetic disorder characterized by reduced or absent melanin synthesis in the skin, hair, and eyes. The resulting hypopigmentation leads to distinctive clinical features, including visual impairment such as nystagmus, photophobia, strabismus, and decreased visual acuity (Neissi *et al.,* 2025). In addition to ocular abnormalities, affected individuals are at increased risk of ultraviolet radiation-induced skin damage and cutaneous malignancies.

Albinism is broadly classified into oculocutaneous albinism (OCA), which affects the skin, hair, and eyes, and

ocular albinism (OA), which primarily involves ocular tissues with minimal or no cutaneous manifestations (Grønskov *et al*., 2007; Witkop, 1989). OCA is genetically heterogeneous and results from pathogenic variants in genes involved in melanin biosynthesis, melanosome formation, or melanosomal transport. To date, several genes have been implicated in nonsyndromic OCA, including *TYR* (OCA1), *OCA2* (OCA2), *TYRP1* (OCA3), and *SLC45A2* (OCA4), among others.

The *TYR* gene encodes tyrosinase, a key enzyme in eumelanin biosynthesis that catalyzes the initial steps of melanin production. Biallelic pathogenic variants in *TYR* cause OCA type 1 (OCA1), which is further subdivided into OCA1A, characterized by complete absence of tyrosinase activity, and OCA1B, associated with partial residual enzyme activity (Hutton and Spritz, 2008). Clinical manifestations may vary depending on the nature of the underlying mutation and residual enzymatic function.

The *OCA2* gene encodes the P protein, which plays a critical role in regulating melanosomal pH and facilitating proper tyrosinase processing and function. Pathogenic variants in *OCA2* result in OCA type 2, one of the most common forms of albinism worldwide. Although clinical features overlap among OCA subtypes, phenotypic variability is frequently observed within and between families (Bjeloš *et al*., 2024; Wei *et al*., 2013; Zaman *et al*., 2024).

Consanguinity significantly increases the prevalence of autosomal recessive disorders, including OCA, in certain populations. Pakistan, where consanguineous unions are common, exhibits a relatively higher burden of inherited conditions. However, data describing the molecular spectrum of OCA in specific ethnic groups remain limited. In this study, we investigated the clinical and molecular characteristics of five consanguineous families of Pakhtun ethnicity affected with nonsyndromic OCA and identified recurrent pathogenic variants in *TYR* and *OCA2*.

MATERIALS AND METHODS

Ethical Approval and Family Recruitment

This study was approved by the Research Ethics Board (REB) of the University of Peshawar, Pakistan (Certificate No. UOP/REB-08/08), in accordance with the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants or their legal guardians for sample collection, clinical evaluation, pedigree construction, and publication of anonymized data and photographs.

Five unrelated consanguineous families, named Family A-E, with multiple affected individuals were enrolled **(Fig. 1)**. Detailed clinical histories were obtained, and physical examinations were conducted. Peripheral blood samples were collected in K_3EDTA tubes and stored under standard conditions until further processing.

DNA Extraction and Whole-Exome Sequencing

Genomic DNA was extracted from the proband of each family using the PureLink® Genomic DNA Mini Kit (Thermo Fisher Scientific, USA) according to the manufacturer's protocol. Whole-exome libraries were prepared using the xGen Exome Research Panel v2 (Integrated DNA Technologies, USA) and sequenced on the Illumina NovaSeq 6000 platform.

Sequencing quality was assessed using FastQC, and low-quality reads were trimmed with Trimmomatic. High-quality reads were aligned to the human reference genome (GRCh37/hg19) using the Burrows-Wheeler Aligner (BWA). PCR and optical duplicates were removed using Picard tools.

Variant Calling and Bioinformatics Analysis

Single nucleotide variants (SNVs) and small insertions/deletions (indels) were identified using GATK HaplotypeCaller (v4). Copy number variation (CNV) analysis was performed using CoNIFER (v0.2.2) and ExomeDepth. Variant annotation was carried out using wANNOVAR. Population frequencies were obtained from gnomAD (v2.1.1), and previously reported clinical interpretations were reviewed using ClinVar and HGMD databases. Additional evidence was assessed through ClinGen resources.

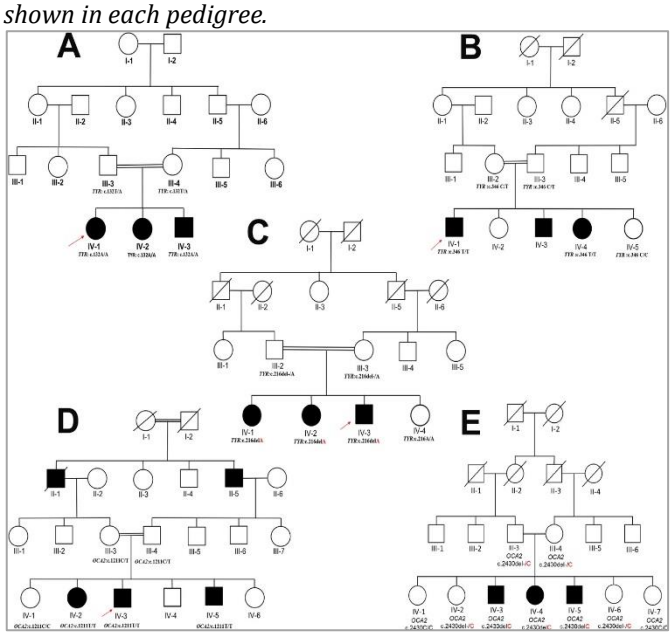
In-silico pathogenicity predictions were retrieved from SIFT, PolyPhen-2, CADD, and MutationTaster. Variants were further evaluated using online interpretation platforms including Franklin (Genoox), VarSome, and GeneBe.

Sanger Sequencing and Variant Classification

Candidate variants identified by whole-exome sequencing were validated by Sanger sequencing. Primers were designed using Primer3Plus, and segregation analysis was performed for all available affected individuals, their parents, and selected unaffected siblings. All variants were manually reviewed and classified according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines (Richards *et al*., 2015).

Figure 1

Pedigrees of albinism families A-E constructed according to standard guidelines by Bennett et al. (2008). All pedigrees demonstrate autosomal recessive mode of inheritance. Affected members are indicated with filled symbols, squares for males and circles for females. The index patient is indicated by the arrow. Genotypes, confirmed via Sanger sequencing, of normal, carrier, and affected members are shown in each pedigree.



RESULTS

Clinical Findings

All affected individuals from the five consanguineous families presented with classical features of nonsyndromic oculocutaneous albinism. Common manifestations included marked hypopigmentation of the skin and hair, iris translucency, nystagmus, photophobia, and reduced visual acuity **(Fig. 2)**. No systemic or syndromic abnormalities were observed in any family.

Families A and B exhibited a typical OCA1 phenotype with uniformly severe hypopigmentation and pronounced ocular involvement. Family C demonstrated striking depigmentation from birth, consistent with a severe clinical presentation. Families D and E displayed phenotypic variability. Nystagmus was variably present in this family, although photosensitivity and visual impairment were consistently reported.

Figure 2

Clinical photographs of affected individuals of enrolled families showing the Oculocutaneous albinism phenotypes.

Molecular Findings

Whole-exome sequencing of the proband from each family identified five recurrent homozygous pathogenic variants in *TYR* and *OCA2* (Fig. 3). Three families (A, B, and C) harbored homozygous variants in the *TYR* gene (NM_000372.5):

Family A: c.132T>A (p.Ser44Arg), missense variant in exon 1.

Family B: c.346C>T (p.Arg116Ter), nonsense variant introducing a premature termination codon.

Family C: c.216delA (p.Val74TrpfsTer46), frameshift variant predicted to result in premature truncation. This variant, although previously reported globally, has not been described in Pakistani patients to our knowledge.

Family D and E exhibited the following two biallelic variants in *OCA2* gene (NM_000275.3):

Family D: c.1211C>T (p.Thr404Met), located in exon 12.

Family E: c.2430delC (p.Phe810LeufsTer7), located in exon 23 causing a frameshift splice region change.

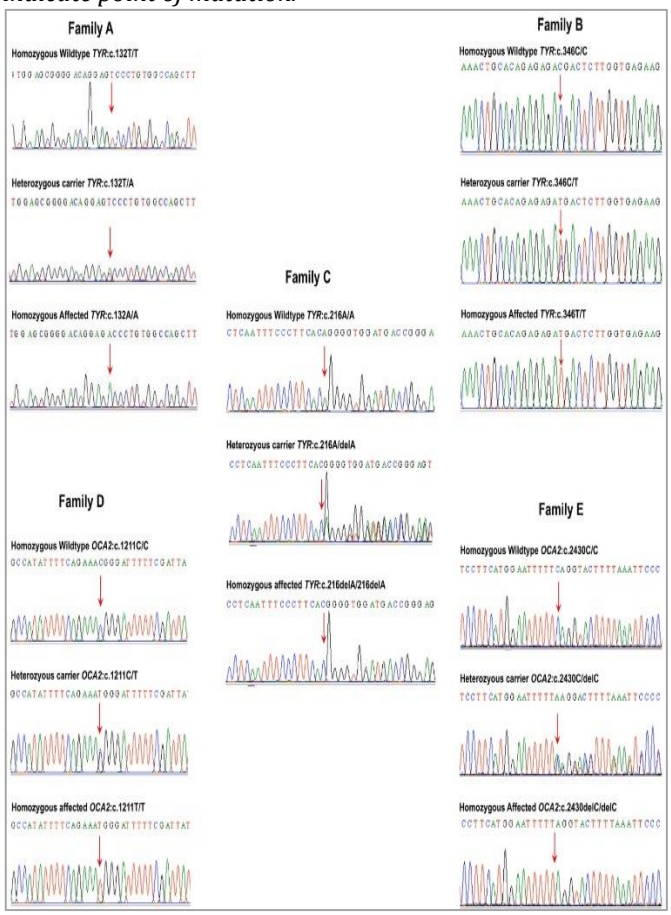
All variants were located in coding regions and were consistent with an autosomal recessive mode of inheritance in these consanguineous families.

Segregation Analysis

Sanger sequencing confirmed complete co-segregation of the identified variants with the disease phenotype in all families. All affected individuals were homozygous for the respective variant alleles, while both parents were heterozygous carriers. Available unaffected siblings carried either the heterozygous state or homozygous wild-type alleles. These findings strongly support autosomal recessive inheritance **(Fig. 3)**.

Figure 3

Sanger sequencing analysis of TYR and OCA2 variants in families A-E respectively. Each family's electropherograms display genotypes of homozygous wildtype, heterozygous carriers, and homozygous affected members. The arrows indicate point of mutation.



In Silico Analysis and ACMG Classification

All identified variants were extremely rare or absent in population databases (gnomAD v2.1.1), with no reported homozygous occurrences. Computational prediction tools (SIFT, PolyPhen-2, CADD, MutationTaster) consistently supported a deleterious effect for the missense variants. The nonsense (p.Arg116Ter) and frameshift (p.Val74TrpfsTer46) variants are predicted to result in premature truncation and likely nonsense-mediated mRNA decay, consistent with loss-of-function, a known disease mechanism for *TYR*. The *OCA2* variant (p.Phe810LeufsTer7) however, was predicted to be likely pathogenic or variant of uncertain significance (VUS).

Previously reported pathogenic status was confirmed through ClinVar and HGMD databases. Variant interpretation platforms including Franklin (Genoox), VarSome, and GeneBe provided concordant classifications. Based on the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines (Richards *et al.,* 2015), the variants were classified into different categories **(Table 1)**.

Table 1
In-silico pathogenicity assessment of prioritized variants across albinism families

Family ID	Gene	Variant (c./p.)	SIFT	PolyPhen-2	Mutation Taster	CADD (Phred)	gnomAD		ACMG Class	ACMG Criteria (Evidence Codes)
							AF	SAS AF		
Fam-A	*TYR*	c.132T>A p.(Ser44Arg)	Deleterious (0.01)	Possibly Damaging (0.873)	Deleterious (86|14)	21.3	0.000019	Absent	Pathogenic	PM2, PP1, PP3, PP5
Fam-B	*TYR*	c.346C>T p.(Arg116Ter)	N/A	N/A	Deleterious (196|4)	34	0.000028	0.000033	Pathogenic	PVS1, PM2, PP1, PP5
Fam-C	*TYR*	c.216delA p.(Val74TrpfsTer46)	N/A	N/A	Deleterious (189|11)	Not found	0.000004	0.000033	Pathogenic	PVS1, PM2, PP1, PP5
Fam-D	*OCA2*	c.1211C>T p.(Thr404Met)	deleterious	Probably damaging (0.999)	Deleterious (59|41)	33	0.000078	Absent	Pathogenic	PM2, PM3, PP1, PP5
Fam-E	*OCA2*	c.2430delC p.(Phe810LeufsTer7)	Not found	Not found	Deleterious (191|9)	Not found	Absent	Absent	Likely pathogenic	PVS1_Strong PM2, PP1

DISCUSSION

In this study, we identified five recurrent homozygous pathogenic and likely pathogenic variants in *TYR* and *OCA2* in consanguineous Pakistani families affected with nonsyndromic oculocutaneous albinism (OCA). Although these variants have been reported previously in other populations, the present study expands their documentation within the Pakistani cohort and confirms their pathogenicity through segregation analysis. Notably, the *TYR* frameshift variant c.216delA (p.Val74TrpfsTer46) has not, to our knowledge, been previously reported in Pakistani patients.

All affected individuals exhibited classical features of OCA, including generalized hypopigmentation, iris translucency, nystagmus, photophobia, and reduced visual acuity. No syndromic manifestations were observed, consistent with nonsyndromic OCA. The clinical severity was relatively uniform among families harboring *TYR* variants, particularly in those with truncating mutations. In contrast, individuals with the *OCA2* missense variant demonstrated variable phenotype. This aligns with the broader phenotypic variability commonly associated with *OCA2*-related albinism (Grønskov *et al*., 2007; Hutton and Spritz, 2008; Ullah, 2022b).

Pathogenic variants in *TYR* are responsible for OCA type 1 (OCA1), a disorder resulting from impaired or absent tyrosinase activity. Tyrosinase catalyzes the rate-limiting steps of melanin biosynthesis, converting tyrosine to dopaquinone, thereby initiating eumelanin production (Oetting, 2000). Loss-of-function variants, such as nonsense and frameshift mutations, typically lead to premature termination codons and nonsense-mediated mRNA decay. This results in complete absence of enzymatic activity and a more severe phenotype (Hutton and Spritz, 2008; Zaman, *et al.,* 2024). In the present study, both the nonsense variant p.Arg116Ter and the frameshift variant p.Val74TrpfsTer46 are predicted to produce truncated proteins, strongly supporting their pathogenic mechanism via haploinsufficiency or complete functional loss.

The missense variant p.Ser44Arg identified in Family A affects a conserved residue within the tyrosinase protein. Missense changes in functionally critical domains of TYR have been shown to impair protein folding, stability, or catalytic activity, leading to reduced melanin synthesis (Mahmood *et al.,* 2020). The consistent phenotype observed in affected individuals further supports the functional significance of this substitution.

The *OCA2* gene encodes the P protein, a transmembrane protein localized to the melanosomal membrane. The P protein regulates melanosomal pH and ionic homeostasis, processes that are essential for proper tyrosinase processing and enzymatic activity. Disruption of melanosomal pH impairs melanin synthesis even in the presence of structurally intact tyrosinase (Johansson *et al*., 2010; You *et al*., 2022). The homozygous p.Thr404Met variant identified in Family D has been previously associated with *OCA2* and is predicted to affect protein structure and function. The comparatively variable pigmentation observed in this family is consistent with prior reports describing phenotypic heterogeneity in OCA2-related albinism (Bao *et al*., 2025; Grønskov *et al*., 2007; You *et al*., 2022).

The predominance of homozygous variants in our cohort reflects the high rate of consanguineous marriages in Pakistan. Autosomal recessive disorders, including OCA, are significantly enriched in populations with frequent intra-familial unions. Previous molecular studies from Pakistan have similarly reported recurrent pathogenic variants in *TYR* and *OCA2*, highlighting their major contribution to OCA in this region (Arshad *et al*., 2018; Shah *et al*., 2022; Zaman *et al*., 2024). The recurrence of specific variants may indicate founder effects or population-specific allele enrichment, although larger cohort studies are required to confirm this hypothesis.

Importantly, all identified variants were extremely rare or absent in population databases and demonstrated complete segregation with disease status within families. The combined genetic and clinical evidence strengthens their pathogenic classification according to ACMG/AMP guidelines (Richards *et al*., 2015).

From a clinical perspective, early molecular diagnosis of OCA is essential for appropriate genetic counseling, carrier detection, and informed reproductive decision-making. In regions with high consanguinity, targeted genetic testing panels incorporating recurrent regional variants may improve diagnostic efficiency and reduce costs.

This study has certain limitations. The sample size was relatively small, and functional assays were not performed to experimentally validate the impact of identified variants. Additionally, broader population-level frequency data for specific ethnic subgroups within Pakistan remain limited. Future large-scale genomic studies are warranted to better define the national mutation spectrum of OCA.

CONCLUSION

This study broadens the mutational spectrum of nonsyndromic oculocutaneous albinism in Pakistani families by identifying recurrent pathogenic variants in *TYR* and *OCA2*. Molecular findings were consistent with clinical presentation and confirmed through segregation analysis. The reporting of these variants in a regional cohort, including one not previously documented from Pakistan, contributes valuable population-specific data. These findings emphasize the importance of molecular diagnosis for accurate counseling and management in genetically heterogeneous and consanguineous populations.

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