ORIGINAL RESEARCH

Mutational Analysis of TYR, OCA2, SLC45A2, and TYRP1 Genes Identifies Novel and Reported Mutations in Chinese Families with Oculocutaneous Albinism

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ABSTRACT

Objective • This study aims to investigate the main types of oculocutaneous albinism (OCA) and the distribution characteristics of mutations in the Chinese population. Additionally, genetic diagnosis and prenatal diagnosis were conducted for Chinese OCA families.

Methods • A total of 116 blood DNA samples were collected from 40 unrelated families with suspected albinism. OCA gene testing and mutation screening were performed to identify mutated genes and genotypes. The prenatal genetic diagnosis was conducted on 20 fetal DNA samples (17 amniotic fluid DNA samples, 2 villus DNA samples, and 1 umbilical cord blood DNA sample). Follow-up was conducted on the born fetuses, and the feasibility and accuracy of prenatal genetic diagnosis were assessed based on the clinical phenotype of the fetuses.

Results • Analysis of 40 pedigrees led to a molecular diagnosis for the patients or their parents: 24 (60%) had OCA1, 12 (30%) had OCA2, 1 (2.5%) had OCA3, and 2 (5%) had OCA4. Furthermore, 2.5% of the patients harbored only one heterozygous mutation in OCA2. The most common form of albinism observed was OCA1, followed by OCA2, OCA4, and OCA3. Prenatal diagnosis was performed on 20 fetuses, and the clinical phenotype of the fetuses aligned with the predictions of prenatal genetic diagnosis after follow-up.

Conclusions • The results of gene mutation analysis in 40 families with oculocutaneous albinism indicate that OCA1 is the predominant type of albinism in the Chinese population, with all four types of OCA identified. Further research is needed to expand the understanding of pathogenic mutations associated with different types of OCA. Prenatal genetic testing, based on determining the albinism type and genotype of the proband and their parents, proves to be the most accurate and least traumatic method in eugenics. This study provides valuable insights into identifying novel therapeutic targets. (*Altern Ther Health Med.* 2023;29(7):278-283).

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The word "Albinism" is derived from the Latin word "albus," meaning white. It represents a heterogeneous group of inherited pigmentation disorders characterized by low or absent melanin in the skin, hair, and eyes. In humans, albinism is attributed to mutations in over twenty different genes.[1] The incidence rate of albinism is approximately 1 in 17 000 individuals, making one in 70 people carriers of the OCA allele.[1] However, the prevalence of specific subtypes varies across populations,[2-4] with OCA1 being the most commonly observed subtype and responsible locus worldwide. Oculocutaneous albinism (OCA), the predominant form of albinism, is an autosomal recessive genetic disorder affecting melanin biosynthesis or transport. OCA represents a significant cause of childhood visual impairment during the early years of life.[5-7]

Clinically, OCAs can be categorized as non-syndromic, affecting only the skin, hair, and eyes, or syndromic, characterized by the presence of additional abnormalities such as immunodeficiency, bleeding tendency, and neurological abnormalities. The non-syndromic form of OCAs is further classified into seven subtypes (OCA1-7), each associated with causative mutations in distinct genes or loci. These include tyrosinase *(TYR)*, OCA2 melanosomal transmembrane protein (*OCA2 or P*), tyrosinase-related protein 1 (*TYRP1*), solute carrier family 45 member 2 (*SLC45A2*), 4q24, solute carrier family 24 member 5 (*SLC24A5*), and leucine-rich melanocyte differentiation-associated protein (*LRMDA*).[8]

The *TYR* gene consists of 5 exons that encode a 529 amino acid enzyme called tyrosinase. This copper-containing enzyme plays a crucial role in melanin biosynthesis. Genetic studies have identified 495 pathogenic mutations in the *TYR* gene, which are associated with OCA1, the most common non-syndromic subtype of oculocutaneous albinism, accounting for approximately 70% of cases in America and China.[9] OCA1 patients exhibit either a complete absence of melanin (type A) or reduced melanin production (type B).

The *OCA2* (*P*) gene comprises 23 coding exons and encodes a P protein consisting of 838 amino acids. This protein acts as a precursor in melanin biosynthesis. Currently, 376 pathogenic mutations have been reported in the OCA2 gene, contributing to OCA2 cases worldwide. The prevalence of OCA2 is approximately 1 in 39 000.[10] The *TYRP1* gene consists of 8 exons and encodes a tyrosinase-related protein 1, which comprises 537 amino acids. This protein plays a vital role in maintaining melanosome structure and proliferation. A total of 68 mutations associated with OCA3 have been identified in the *TYRP1* gene. OCA3 is less prevalent compared to OCA1 and OCA2.[11]

The *SLC45A2* (*MATP*) gene comprises 7 exons and encodes a 530 amino acid protein called MATP. This protein is believed to be crucial for melanosome function and pigmentation. Genetic analysis of various OCA4 families has revealed 181 pathogenic mutations in the *SLC45A2* gene. OCA4 accounts for approximately 24% of OCA cases.[12] The *SLC24A5* gene consists of 9 exons and encodes a 500 amino acid protein called solute carrier family 24 member 5 protein. This protein plays a significant role in the maturation of melanosomes, and deficiencies in *SLC24A5* can disrupt melanin synthesis. To date, 32 mutations have been identified in various OCA6 families, contributing to the manifestation of this subtype.[13]

The *LRMDA* (*C10orf11*) gene[8] comprises 7 exons and encodes a leucine-rich melanocyte differentiation-associated protein consisting of 226 amino acids. The LRMDA protein is involved in melanocyte differentiation. A total of 12 pathogenic mutations have been reported in the *LRMDA* gene, leading to the development of OCA7, see Table 1. OCA5 has been mapped to chromosome 4q24; however, the causative gene responsible for this subtype has not yet been identified.[8,9] OCA6 and OCA7 are considered very rare, with only a few families reported for these specific OCA subtypes. Additionally, OCA5 has only been reported in Pakistani families.[9]

This paper aims to investigate the main types of OCA and the distribution characteristics of mutations within the Chinese population. Additionally, genetic diagnosis and prenatal diagnosis were conducted for Chinese families with OCA.

METHODS

Study Population

A total of 136 individuals from 40 families were recruited for this study at the Department of Medical Genetics, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, China. Inclusion criteria involved unrelated individuals with clinical indications of ocular skin albinism, while exclusion criteria included a loss to follow-up via telephone. Written informed consent was obtained from all participants or their legal guardians, and the study was conducted following the principles outlined in the Declaration of Helsinki, with approval from the University's Ethical Committee.

DNA Isolation and Collection

The inclusion criteria for this study involved the presence of skin and eye symptoms. In the Chinese population, normal pigmentation is characterized by black hair, black eye color, and yellow skin color. A total of 40 families were screened for participation. Initially, patients were screened through *TYR*, *OCA2*, *SCL45A2*, and *TYRP1* genes DNA sequencing. In cases where no abnormalities were detected, whole exome sequencing was employed. Patients presenting with syndromic albinism, such as immune system abnormalities, symptoms affecting other organs, or ocular symptoms only (ocular albinism), were excluded from the study.

Approximately 2 ml of venous blood samples or 20 ml of amniotic fluid samples were collected from the recruited family members for DNA sequencing analysis. A total of 136 individuals from 40 isolated OCA families in China were included in the analysis. Genomic DNA was isolated from blood samples using a DNA extraction kit (Beijing TIANGEN Company), while the DNA Kit from the same company (Beijing TIANGEN Company) was utilized for fetal DNA isolation.

PCR Analysis and Sequencing *TYR, OCA2, SCL45A2* and *TYRP1* Genes

Polymerase chain reaction (PCR) and sequencing were performed to analyze the *TYR, OCA2, SCL45A2*, and *TYRP1* genes. Primers for amplification were designed using the primer3plus online database (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi), targeting all exons and exon/intron junctions. The PCR reaction mixture included 25 ng of genomic DNA, 1 µl of each primer, 13 µl of 2× Green Master-Mix, and PCR H_2O to a total volume of 25 µl cocktail. The PCR amplification program consisted of an initial denaturation step at 95°C for 10 minutes, followed by 35 cycles of denaturation at 95°C for 1 minute, annealing at 57 to 62°C (depending on the primer) for 1 minute, extension at 72°C for 1 minute, and a final extension step at 72°C for 10 minutes. The PCR products were visualised by 2% agarose gel electrophoresis and ethidium bromide staining. The PCR amplicons were subjected to bidirectional sequencing using a DNA Sequencer.

Mutational Analysis

The sequencing chromatograms were analyzed to identify pathogenic variations by comparing them with the normal sequence obtained from the UCSC Genome Browser (https://genome.ucsc.edu/). Bioedit software was utilized for chromatogram analysis. In order to confirm the presence of a single nucleotide polymorphism or pathogenic variant in

Table 1. HGMD genes and mutations associated with OCA

OCA	Gene	Gene Description	OMIM #	Chromosome Location	Mutations
OCA1	TYR	Tyrosinase	606933	11q14-q21	495
OCA2	P	OCA2 melanosomal transmembrane protion	611409	15q11.2-q12	376
OCA3	TYRP1	Tyrosinase-related protein 1	115501	9p23	68
OCA4	SLC45A2	Solute carrier family 45 members 2	606202	5p13.3	181
OCA5	UK	----	615312	4q24	1
OCA6	SLC24A5	Solute carrier family 24 members 5	609802	15q21.1	32
OCA7	LRMDA	Leucine-rich melanocyte differentiation associated	614537	10q22.2-q22.3	12

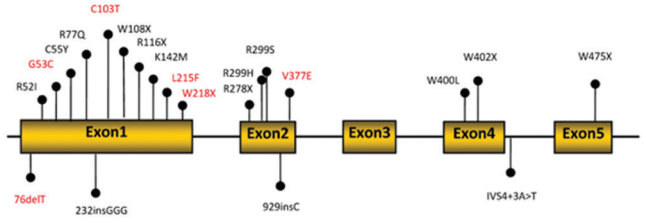
Note: The information presented in this table is derived from the Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk) and the Online Mendelian Inheritance In Man (OMIM) database (https://omim.org/), as of June 30th, 2020. The gene descriptions, OMIM numbers, chromosomal locations, and number of mutations are provided for each OCA subtype. Please note that OCA5 is listed as "UK" (unknown) regarding the associated gene.

Table 2. Genotypes and Mutations for 40 Chinese Families with Patients of Oculocutaneous Albinism

Family No.	Clinial Diagnosis	Proband Genotype	Paternal Genotype	Maternal Genotype	Proband other Family member Genotype	Fetal Genotype
1	OCA2	T450M/G775R	G775R	T450M		
2	OCA2	163delG/Q596X	Q596X	163delG	siser163delG/Q596X	
3	OCA2	R419W/S788L	R419W	S788L		
4	OCA2	T482A/L622P	T482A	L622P		
5	OCA1	K142M/K142M	K142M	K142M	uncle N/N	K142M/K142M
6	OCA2	T450M/P743L	--	--	son P743L/N	
7	OCA2	IVS7-3C>G/IVS11+1G>A	IVS7-3C>G	IVS11+1G>A		N/N
8	OCA2	T404M/R572C	T404M	R572C		
9	OCA1	R299H/929insC	R299H	929insC		c.929insC/N
10	OCA4	562-(1118±2)del6365bp/562-(1118±2)del6365bp	562-(1118±2)del6365bp	562-(1118±2)del6365bp	wife N/N	
11	OCA1	R116X/R142M	--	--		N/N
12	OCA1	R116X/R278X	R116X	R278X		R278X/H
13	OCA2	I473S/?	I473S	N	sister N/?	
14	OCA1	G53C/V377E	V377E	G53C		G53C/N
15	OCA1	R52I/232insGGG	232insGGG	R52I		N/N
16	OCA1	W108X/W400L	W400L	W108X		
17	OCA1	R402X/IVS4+3A>T	--	--		R402X/N
18	OCA1	R299S/R299S	R2995	R2995	sister R299S/N	
19	OCA2	c.167delC/IVS11+1G>A	c.167delC	IVS11+1G>A		
20	OCA1	R278X/W400L	R278X	W400L		R278X/W400L
21	OCA4	D160H/c.563delG	c.563delG	D160H		
22	OCA1	c.232insGGG/R278X	c.232insGGG	R278X		N/N
23	OCA1	R77Q/W400L	R77Q	W400L		W400L/N
24	OCA1	C103T/c.929insC	C103T	c.929insC		C103T/N
25	OCA1	R77Q/W400L	--	--	niece N/N	
26	OCA1	R77Q/W400L	W400L	R77Q		
27	OCA1	R77Q/R299H	R299H	R77Q		N/N
28	OCA2	R419W/P740L	--	--		P743L/N
29	OCA1	C55Y/W475X	W475X	C55Y		
30	OCA1	76deIT/c.929insC	C.929insC	c.76delT		
31	OCA1	L215F/R402X	R402X	L215F		
32	OCA1	R299S/R299H	R299S	R299H	sister R299H	
33	OCA1	c.929insC/c.929insC	c.929insC	c.929insC		c.929insC/c.929insC
34	OCA2	c.2165delT/M748I	--	--		c.2165delT/N
35	OCA3	R87Q/G204X	R87Q	G204X	Siser G204X	G204X/N
36	OCA1	c.232insGGG/R299H	R299H	c.232insGGG		N/N
37	OCA2	IVS11+1G>A/A481T	A481T	IVS11+1G>A		
38	OCA2	IVS7-3C>G/F505S	F505S	IVS7-3C>G	sisterIVS7-3C>G/N	IVS7-3C>G/N
39	OCA1	R299H/c.929insC	--	--		R299H/N
40	OCA1	c.232icGGG/W218X	W218X	c.232insGGG		

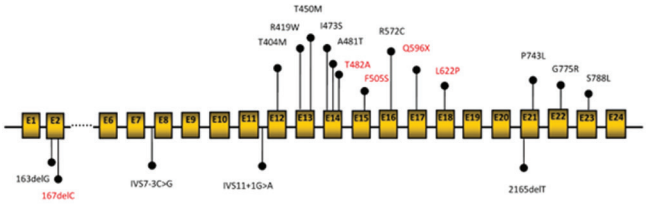
Note: This table provides information on the clinical diagnosis, genotypes of probands, paternal genotypes, maternal genotypes, genotypes of other family members, and fetal genotypes for the analyzed Oculocutaneous Albinism (OCA) families. "N" indicates the wild-type genotype, while "?" denotes an unknown genotype. The genotypes are presented for each family; in cases where the genotype is unavailable, it is indicated as "--".

Figure 1. Schematic diagram of 21 mutations detected in *the TYR* gene



Note: The figure illustrates the distribution of 21 mutations detected in the *TYR* gene. Missense mutations are depicted on the horizontal line, while frameshift or shear site mutations are shown on the lower line. Unreported mutations are represented in red font, while reported mutations are represented in black font.

Figure 2. Schematic diagram of 18 mutations detected in the *P* gene.



Note: The figure presents a schematic diagram depicting the distribution of 18 mutations detected in the P gene. Missense mutations are represented on the horizontal line, while frameshift or shear site mutations are indicated on the lower line. Unreported mutations are highlighted in red font, while reported mutations are displayed in black font.

Figure 3. Schematic diagram of 18 mutations detected in the *TYRP1* gene

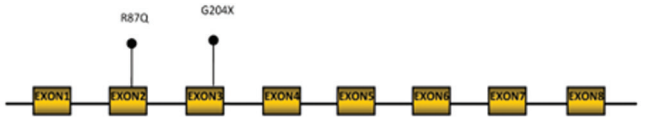
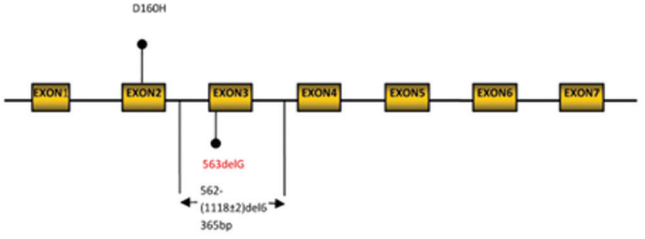


Figure 4. Schematic diagram of 3 mutations detected in *SLC45A2* gene



the relevant gene of the suspected OCA family, approximately 100 control samples from phenotypically healthy individuals of the same ethnic group were randomly selected, and their genomic DNA was sequenced. The pathogenicity of the identified single nucleotide polymorphisms was predicted using the SIFT (https://sift.bii.a-star.edu.sg/) and PolyPhen (http://genetics.bwh.harvard.edu/pph2/) databases.

RESULTS

Type of OCA Gene Mutations

A total of 136 individuals from 40 families were analyzed for mutations in the relevant OCA genes (Table 2). Among them, 24 families (Family no. 5, 9, 11-12, 14-18, 20-27, 29-33, 36, and 39) were found to have segregating mutations in the *TYR* (OCA1) gene, while 14 families (Family no. 1-4, 6-8, 13, 19, 28, 34, 37, 38, and 40) were associated with *OCA2* (*P*) mutations (Table 2). Family 35 was diagnosed with *TYRP1* (OCA3) mutations, while family 10 had *MATP* (*SLC45A2*; OCA4) gene mutations. In all cases, the OCA patients exhibited an autosomal recessive pattern of inheritance, with their parents being genotypically heterozygous carriers of the mutations, as confirmed through family member testing, see Table 2.

Proportion of Mutations in Each Type of OCA

A comprehensive analysis of 40 pedigrees led to a molecular diagnosis for either the patients or their parents, revealing the following distribution: 24 (60%) with OCA1, 12 (30%) with OCA2, 1 (2.5%) with OCA3, and 2 (5%) with OCA4. Furthermore, 2.5% of the patients exhibited a single heterozygous mutation in OCA2. It is noteworthy that OCA1 is the most prevalent form of albinism, followed by OCA2, OCA4, and OCA3, respectively.

Reported and Unreported Mutations

In this study, a total of 21 mutations in the *TYR* gene were identified, comprising 15 reported mutations and 6 previously unreported mutations (c.76delT, G53C, C103T, W108X, L215F, V377E) (Figure 1). Additionally, 18 mutations were detected in the *P* gene, of which 13 were reported mutations and 5 were previously unreported (c.167delC, T482A, F505S, Q596X, L622P) (Figure 2). Two mutations in the *TYRP1* gene were identified, which have already been published in 2022[10] (Figure 3). Furthermore, 3 mutations in the *SLC45A2* gene were detected, including 2 reported mutations and 1 previously unreported mutation (c.563delG) (Figure 4).

Prenatal Genetic Diagnosis Results in 20 Fetal Tissues

The results of prenatal genetic diagnosis conducted on 20 fetal tissues (Table 1) revealed that 3 fetuses were diagnosed with OCA, 11 fetuses tested positive as heterozygotes for gene mutations, and 6 fetuses were confirmed to be normal. Notably, the postnatal follow-up results aligned with the predictions made during prenatal genetic diagnosis.

DISCUSSION

Oculocutaneous albinism is characterized by a reduction or complete absence of melanin synthesis, despite the presence of structurally normal melanocytes in the skin, hair, and eyes. This condition follows a recessive hereditary trait.[11] The pathogenesis of albinism has been linked to various gene mutations such as TYR, OCA2, SLC45A2, and TYRP1. Albinism has been studied for many years as a congenital and rare disease without a cure. Individuals born with albinism risk developing various complications, including blindness, skin carcinoma, melanoma, and other related conditions.[12]

This situation has undergone a significant transformation and will continue to improve due to the discovery of these underlying gene mutations, providing novel therapeutic targets. While oculocutaneous albinism can be found in all ethnic groups, most discoveries have been made within the Caucasian population. Despite the numerous reported pathological findings associated with OCA, our understanding of the underlying molecular mechanisms remains limited. To develop effective therapeutic approaches, it is crucial to gain comprehensive insights into the molecular mechanisms, elucidate their detailed structural and functional characteristics, and ascertain the prevalence of these mutations among Chinese albinism patients.

In this study, we conducted an analysis of relevant gene mutations in a cohort of 136 individuals from 40 families. Our findings revealed that 24 families exhibited segregating *TYR* (OCA1) gene mutations, while *OCA2* (*P*) mutations were identified in 13 families. Additionally, one family showed *TYRP1* (OCA3) mutations, and two families presented with *SLC45A2* (OCA4) mutations (Table 2). As expected, all individuals with OCA demonstrated a pattern of autosomal recessive inheritance, with their parents being genotypically heterozygous carriers of the mutations, see Table 2.

We identified a total of 21 mutations in the *TYR* gene, accounting for 47.7% of the detected mutations. Among these were 12 missense mutations, 6 nonsense mutations, and 3 insertion/deletion mutations. Additionally, we identified 18 mutations in the *P* gene, accounting for 40.9% of the detected mutations. These included 14 missense mutations, 1 nonsense mutation, and 3 insertion/deletion mutations. We detected two mutations in the *TYRP1* gene, accounting for 4.5% of the total mutations. These mutations consisted of one missense mutation and one nonsense mutation. Furthermore, we found three mutations in the *MATP* gene, accounting for 6.8% of the total mutations. These mutations included one missense mutation and two insertion/deletion mutations. Based on these findings, it is likely that OCA1 is the predominant pathogenic type of albinism in China. Additionally, missense mutations appear to be the most common mutation type leading to OCA.

The aim of screening and analyzing mutation genes in albinism is to enhance the accuracy of prenatal gene diagnosis and facilitate improved prenatal genetic consultation and care for both prenatal and postnatal stages. Based on the identification of pathogenic genes in probands with albinism, prenatal gene diagnosis was performed using 20 fetal tissue samples (17 cases of amniotic fluid, 2 cases of villi, and 1 case of umbilical cord blood). The results revealed that 3 fetuses had OCA, 11 individuals were carriers of the OCA gene mutation, and 6 cases were genetically normal. Importantly, the clinical phenotypic results obtained from postnatal follow-up were consistent with the prenatal genetic diagnosis.

We observed that the clinical manifestations of oculocutaneous albinism varied slightly across different gene mutations but were more closely associated with disease activity. Specifically, patients with TYR mutations could be classified into two subsets. The OCA1A subset exhibited a loss of melanin in the skin, hair, eyelashes, eyebrows, and completely translucent irises. These individuals often experienced significant visual impairment, photophobia, and the presence of amelanotic nevi. Importantly, we noted that the symptoms of these patients did not vary with age or race. On the other hand, OCA1B was characterized by a milder disease presentation, with pigment loss in the hair, skin, and irises, often appearing as green or brown. Visual impairment was still present but was generally better than in patients from subset 1.

Although there was variation in the degree of cutaneous pigment and iris color, our data indicated that patients with OCA2 mutations consistently exhibited pigmented hair. Nevi and freckles were frequently observed on the skin. Furthermore, visual acuity in OCA2 mutation patients was generally better compared to those with OCA1 mutations, often reaching 3/10. Interestingly, we noted similar presentations in patients with TYRP1 mutations. This similarity suggests a potential shared downstream molecular pathway between these two mutations.

It is well established that OCA3 (TYRP1) mutations are predominantly observed in individuals of African descent but are rarely found in other ethnic populations. In particular, individuals of Chinese ethnicity with yellow skin are more prone to misdiagnosis. This discrepancy contributes to the relatively small proportion of OCA3 cases identified within the Chinese population. Our study identified a single case of OCA3, which presented with nonspecific symptoms. Consequently, differential diagnosis can be challenging for such patients, especially within the Asian population.

Study Limitations and Future Directions

Our study findings suggest that the classification of oculocutaneous albinism in Chinese patients aligns with the published guidelines predominantly based on other ethnic groups. However, it is important to acknowledge the limitations of our study, primarily the restricted sample size. Future studies should encompass larger patient populations and involve multiple study centers to validate and further explore our results. These efforts will enhance the robustness and generalizability of the findings, providing a more comprehensive understanding of oculocutaneous albinism in the Chinese population.

CONCLUSION

Our study expands the existing evidence on the prevalence of TYR and OCA2 gene mutations in Chinese families affected by oculocutaneous albinism. We identified TYRP1 and SLC45A2 gene mutations, albeit at lower frequencies, suggesting their contribution to the genetic etiology of albinism in this population. Furthermore, our study highlighted the heterogeneity in clinical manifestations among patients with different gene mutations, emphasizing the need for personalized approaches in diagnosis and management. Identifying *TYR* as the most commonly mutated gene in Chinese patients aligns with previous reports in other populations, indicating a conserved genetic basis for oculocutaneous albinism across diverse ethnic groups. This knowledge is crucial for improving genetic counseling, facilitating early diagnosis, and developing targeted therapies. The comprehensive understanding of the genetic mutation landscape achieved in this study opens avenues for future research on novel therapeutic targets, potentially leading to breakthroughs in treating albinism and associated complications.

STATEMENT

Mutation in Family 10 has already been reported by our group in 2012 (Xu B, Pang T, Yao CQ, et al. Zhonghua Yi Xue Za Zhi. 2012;92(4):254-258. https://pubmed.ncbi.nlm.nih.gov/22490798/) Our group has already reported mutation in Family 35 in 2022 (Xu B, Li HY. Novel Mutations in the TYRP1 Gene in Oculocutaneous Albinism Type III in a Chinese Family [J/OL]. CMCR, 2022, 04(1): E06491-E06491.)

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS STATEMENT

This study was approved by the Zhongshan School of Medicine, Sun Yat-sen University Ethical Committee and performed according to the principles of the Declaration of Helsinki.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR'S CONTRIBUTIONS

BX and HL designed the study and performed the experiments, BX and XC collected the data, HL and XC analyzed the data, and BX and HL prepared the manuscript. All authors read and approved the final manuscript.

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