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ORIGINAL ARTICLE

Novel compound heterozygous mutations in *OCA2* gene were identified in a Chinese family with oculocutaneous albinism

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Abstract

Background: Oculocutaneous albinism (OCA) is a group of rare autosomal recessive disorders characterized by clinical genetic heterogeneity. OCA type II (OMIM: 203200) is the most common subtype among African and African Americans, primarily caused by pathogenic variants in the *OCA2* (HGNC ID: 8101) gene. In this study, we presented a Chinese family with OCA and reported two novel variants in the *OCA2* gene.

Methods: Whole-exome sequencing (WES) was performed to identify pathogenic variants in the proband. The candidate variants were subsequently validated using Sanger sequencing and QPCR assay. Additionally, bioinformatics analyses were employed to predict the deleteriousness and conservation of the identified mutations.

Results: In the 16-year-old male proband, two novel compound heterozygous *OCA2* variants, NM_000275.3: c.1640T>G (NP_000266.2: p.L547R) and an exons 10-19 deletion variant, were identified. Meanwhile, a reported heterozygous variant c.1441G>A/p.A481T (NM_000275.3, NP_000266.2) in the *OCA2* gene was also found in the proband. Sanger sequencing confirmed that the two variants c.1441G>A/p.A481T and c.1640T>G/p.L547R were inherited from his father. Moreover, qPCR assay revealed that the exons 10-19 deletion was inherited from the mother, his sister also carried this variant. Fortunately, the variant was not detected in the amniotic fluid of the proband's sister. Multiple online bioinformatics tools predicted the variant c.1640T>G to be damaging, leading to the replacement of a highly conserved leucine with an arginine. The gross exon 10-19 deletion in the *OCA2* gene resulted in a truncated, non-functional protein losing the 3–9 transmembrane α-helices domains. According to the American College of Medical Genetics and Genomics classification, these three variants in the *OCA2* gene were evaluated as likely pathogenic.

Conclusion: This study has identified two novel compound variants in the *OCA2* gene and a previously reported variant in a Chinese family with OCA. By expanding the mutation spectrum of the *OCA2* gene, our findings contribute to a better understanding of the genetic basis of OCA.

KEYWORDS
mutation, *OCA2*, oculocutaneous albinism, whole-exome sequencing

1 | INTRODUCTION

Oculocutaneous albinism (OCA) is a group of rare autosomal recessive disorders with clinical genetic heterogeneity. It is characterized by reduced pigment in the eyes, skin, and hair due to the deficiency in melanin synthesis, leading to ocular abnormalities such as poor vision, nystagmus, and an increased risk of light damage and skin cancer (Fábos et al., 2017). The prevalence of OCA is about 1/17,000 globally and 1/18,000 among the Chinese Han population (Grønskov et al., 2007; Wang et al., 2015). However, the prevalence of OCA subtypes varies greatly among different ethnic populations. OCA type I (OCAIA, OMIM: 203100; OCAIB, OMIM: 606952) is the most common subtype in Caucasians, accounting for approximately 50% of global cases (Chuan et al., 2021; Hutton & Spritz, 2008). In African and African Americans, OCA type II (OMIM: 203200) is the most common subtype, with an estimated prevalence of 1:10,000 in African Americans (Rooryck et al., 2008). Among the Chinese Han population, the overall prevalence of OCA is about 1:18,000, with OCA type I being the most common subtype at 70.1% and OCA type II accounting for 10.2% (Wei et al., 2010).

OCA2 (HGNC ID: 8101), also known as *P* gene, is located on 15q11.2-q12 and encodes a melanosome-specific transmembrane protein. Causative variants in *OCA2* were found to be the most common in pediatric patients with OA/OCA in the United States, representing 28% of cases (Chan et al., 2023). *OCA2* is involved in the transport of tyrosine, stabilizing the melanosome protein complexes, regulating the pH of melanosome and the glutathione metabolism, and maintaining the stability of tyrosinase, all of which are essential for melanin synthesis (Lee et al., 2021; Montoliu et al., 2014; Yuasa et al., 2007). The identified *OCA2* pathogenic variants include missense/nonsense single nucleotide variants (SNVs), splicing variants, and small and large indels (Chan et al., 2021). A total of 344 variants of the *OCA2* gene associated with OCA type II have been reported in the HGMD database (Q2 2023. https://www.hgmd.cf.ac.uk/ac/index.php, Supplementary Table S2), and novel variants are still being discovered.

In clinical diagnosis, identifying OCA is relatively straightforward due to the significant reduction of melanin in the skin and hair. However, distinguishing between different OCA subtypes can be challenging due to their overlapping and varied manifestations. Genetic analysis is crucial for determining the genetic etiology of patients and achieving accurate diagnosis and genetic counseling of the OCA subtype. In this study, we performed whole-exome sequencing (WES) analysis to provide an accurate genetic diagnosis for a 16-year-old male patient with OCA from a Chinese family. Through WES, three variants of the *OCA2* gene were identified in the proband, which may potentially explain the clinical presentations of OCA.

2 | MATERIALS AND METHODS

2.1 | Clinical features and ethical approval

A 16-year-old male patient presented with albinism phenotype was recruited for the study. The study was approved by the Ethics Committee of Hefei First People's Hospital and followed the Helsinki protocols. After obtaining informed consent from the family, the peripheral blood samples of the patient, his parents, and sister were collected. Additionally, at the request of the elder sister, amniotic fluid was collected to verify whether the fetus carried pathogenic mutations.

2.2 | WES analysis

The genomic DNA was isolated from peripheral blood samples using the Magnetic Universal Genomic DNA Kit (TIANGEN, China). DNA libraries were constructed, and exome capture was performed using the IDT xGen Exome Research Panel v 1.0 (Integrated DNA Technologies, Coralville, Iowa, USA) with the isolated genomic DNA. Subsequent high-throughput sequencing was carried out using an Illumina NovaSeq 6000 machine (Illumina, CA, USA). The WES sequencing was conducted by Yinfeng

Gene Technology Co., Ltd. (Jinan, China), and both samples had an average coverage depth of 100-fold. GATK (DePristo et al., 2011) was used to call SNVs and indels from the raw data after removing low-quality reads, which were then annotated by ANNOVAR (Wang et al., 2010).

The called variations with a minor allele frequency (MAF) less than 0.01 in the 1000 Genomes Project, ExAC, and gnomAD databases were included for further analysis. The bioinformatics databases MutationTaster (MT, https://www.mutationtaster.org/), SIFT (https://sift.bii.a-star.edu.sg/index.html), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), GERP++, CADD, Revel score, and M-CAP (http://bejerano.stanford.edu/MCAP/) were utilized to predict the deleteriousness and conservation scores of the variants. Finally, the pathogenicity of the variants was evaluated according to the American College of Medical Genetics (ACMG) guidelines (Richards et al., 2015).

2.3 | Sanger sequencing

The candidate variants were further confirmed by Sanger sequencing. The genomic DNA extracted in the previous step was used as a template for PCR amplification. The primers were as followers: *OCA2* (c.1441, NM_000275.3): F: 5′-AGTTGTTCATTCCCCCCAGC-3′, R: 5′-TCCCAGTC TTGAGATGCCCA-3′; *OCA2* (c.1640, NM_000275.3): F: 5′-ATGCTATCCCTGCCCCCTA-3′, R: 5′-CTGGTTTTGTG TTGTTTCTTTGG-3′. The PCR product was sequenced by Yinfeng Gene Technology Co., Ltd.

2.4 | QPCR analysis

The deletion of *OCA2* exons 10-19 was further confirmed by analyzing the copy number of *OCA2* exons using qPCR. Primers were designed to map exon 15 of *OCA2* (NM_000275.3). Specifically, the primers used were OCA2-F: 5′-AGCAGAGTAGACAGGGTGGGG-3′ and OCA2-R: 5′-AAGGAATTTAGTCGGGAGGGAT-3′. The *GAPDH* was used as the reference gene. The qPCR reaction was carried out using a ChamQ Universal SYBR qPCR Master Mix (Vazyme, Nanjing, China) with the Applied Biosystems StepOne Plus Real-time PCR system (ABI, Thermo Fisher, USA). Copy number was calculated using the ΔΔCt method. Negative controls were included using genomic DNA samples from two normal individuals. The relative copy number observed for the normal samples was approximately 1, while for the heterozygous *OCA2* exon deletion samples, it was about 0.5. Likewise, for the homozygous *OCA2* exon deletion samples, the relative copy number was around 0.

2.5 | In silico analysis

Multiple amino acid sequences of the *OCA2* gene from different species were obtained from the Uniprot database (https://www.uniprot.org/) and analyzed using MEGA software. SWISS-MODEL was used to simulate protein structural models for both the wild-type and mutated forms of OCA2 proteins.

3 | RESULTS

3.1 | Clinical outcomes

The 16-year-old male proband (II-2) is the second child of an unrelated non-consanguineous family (Figure 1a). The patient presents with a distinct albinism phenotype, including white skin, yellowish-white hair, white eyelashes, and blue pupils accompanied by nystagmus. At the time of treatment, his sister, who was 18-gestational-week pregnant, showed no abnormality.

3.2 | WES analysis and Sanger sequencing validation

WES was performed in the proband with a depth of 100× to identify the etiology. In total, 1533 SNPs and indels were screened with a MAF of less than 0.01 deposited in the dbSNP, gnomAD database, 1000 Genome Project (1000 G), and NHLBI Exome Sequencing Project (ESP). Two missense variants and a deletion variant in the *OCA2* gene were identified in the proband. The first variant identified was NM_000275.3: c.1441G>A (rs74653330, p.Ala481Thr/p.A481T, NP_000266.2) in exon 14 of the *OCA2* gene, which has been well reported with OCA (Yuasa et al., 2007). The second variant identified was a novel variant (NM_000275.3: c.1640T>G, p.Leu547Arg/p.L547R) in exon 16 of the *OCA2* gene. Finally, a gross heterozygous deletion with exons 10-19 in the *OCA2* gene was also detected.

The variants c.1640T>G and exons 10-19del were not identified in the gnomAD, ExAC, or 1000 Genomes database, as well as ClinVar database. The variant c.1441G>A has been included in the 1000 Genomes, dbSNP, and gnomAD databases with an allele frequency of 0.03389 in East Asian in gnomAD. According to the American College of Medical Genetics and Genomics (ACMG), the variant c.1640T>G (p.L547R) in *OCA2* gene was classified as likely pathogenic (PM1+PP3_Moderate+PM2_Supporting+PP4), the variant c.1441G>A (p.A481T) was classified as likely pathogenic (PM1+PM3+PS3_Supporting+PP3+PP4), and the exon 10-19del variant was classified as likely pathogenic (PVS1_Strong+PM3+PM2_Supporting+PP4).

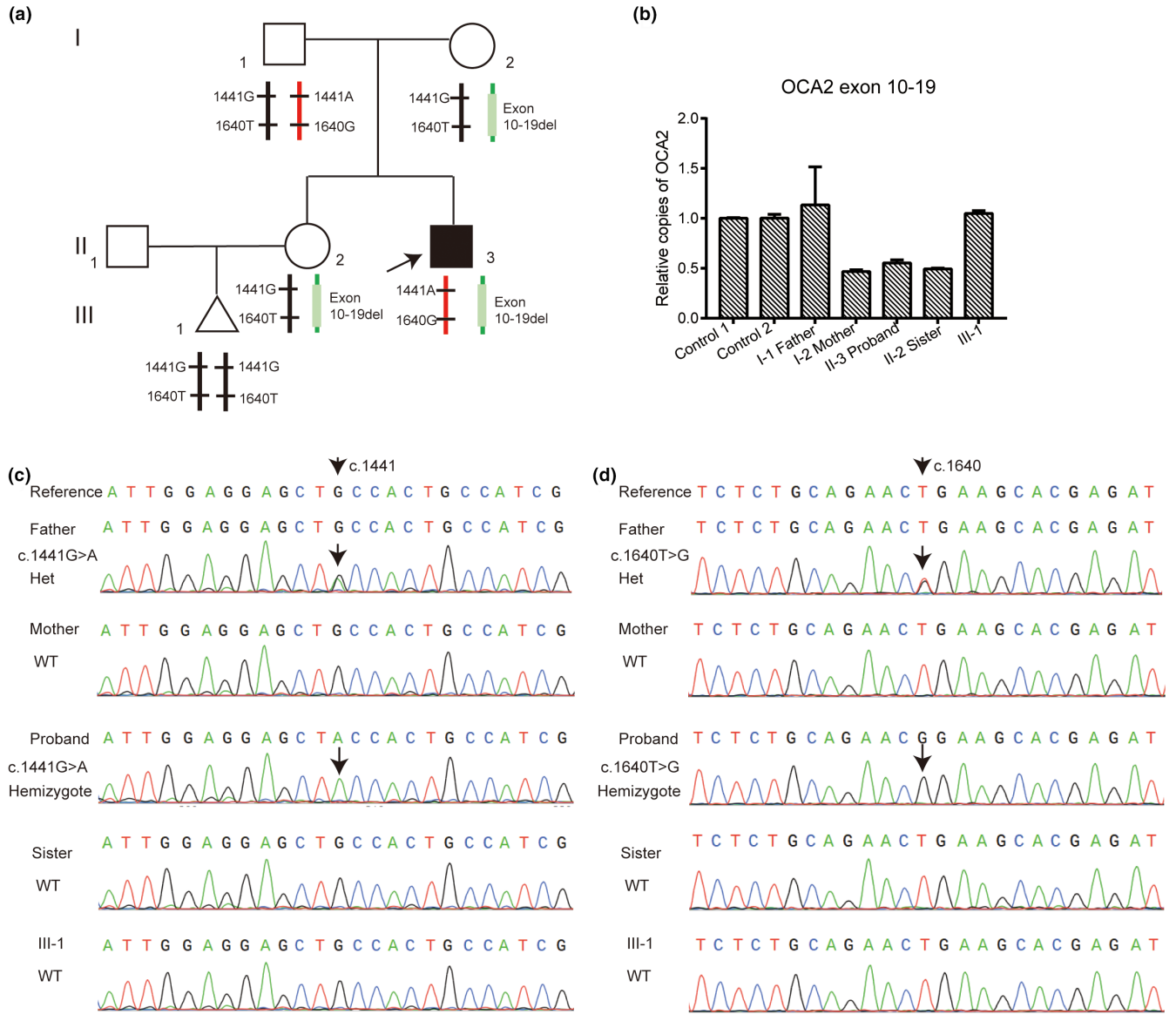

FIGURE 1 The pedigree and variants validation. (a) Pedigrees of the Chinese family with OCA. Squares and circles indicate males and females, respectively. Triangle represents fetus. Arrows indicate the proband. (b) Confirmation of exons 10–19 deletion using qPCR assay. The proband and his sister both inherited the gross deletion from the mother. (c) and (d) Sanger sequencing showed that the patient inherited the c.1441G>A and c.1640T>G variants from his father, his sister was wild-type.

To further verify the three variants identified by WES, Sanger sequencing and qPCR were used. As shown in Figure 1b, the copy number of exons 10-19 detected in the proband was consistent with that of the mother and the sister, which was almost half of the father and control samples, indicating that this variant of the proband was inherited from his mother. Fortunately, the sister fetus did not inherit the mutation (Figure 1b). Sanger sequencing confirmed that the c.1441G>A and c.1640T>G variants of the proband were inherited from his father, and his mother and sister were wild-type, as well as the fetus (Figure 1c,d). Furthermore, these data suggested that the c.1441G>A and c.1640T>G variants inherited from the father were likely to be on the same allele and combined with the exons 10-19 deletion variant to form compound heterozygous variants of the *OCA2* gene in the proband.

3.3 | Pathogenic assessment

To further evaluate the pathogenesis of the three variants in the *OCA2* gene, bioinformatic programs were performed. The results from different prediction tools showed that the variant c.1441G>A (p.A481T) was predicted to be "Damaging/Deleterious/Probably damaging/Disease-causing automatic" by FATHMM, LRT, Polyphen-2, and Mutation Taster, but predicted to be "Tolerated" by SIFT and BayesDel addAF (Table 1). Similarly, all prediction

TABLE 1 In silico prediction of OCA2 p.A481T and p.L547R mutations.

p.A481T			p.L547R		
Engine	**Prediction**	**Score**	**Engine**	**Prediction**	**Score**
BayesDel addAF	Tolerated	0.4381	BayesDel addAF	Damaging	0.9241
MetaRNN	Tolerated	0.003019	MetaRNN	Damaging	0.87
REVEL	Pathogenic	0.72	REVEL	Pathogenic	0.9732
FATHMM	Damaging	0.8281	FATHMM	Damaging	0.9196
LRT	Deleterious	0.8433	LRT	Deleterious	0.8433
SIFT	Tolerated	0.2099	SIFT	Damaging	0
Polyphen-2	Probably damaging	0.466	Polyphen-2	Probably damaging	0.997
Mutation Taster	Disease-causing automatic	0.5367	Mutation Taster	Disease-causing	0.81
PROVEAN	Neutral	0.4818	PROVEAN	Damaging	0.8776

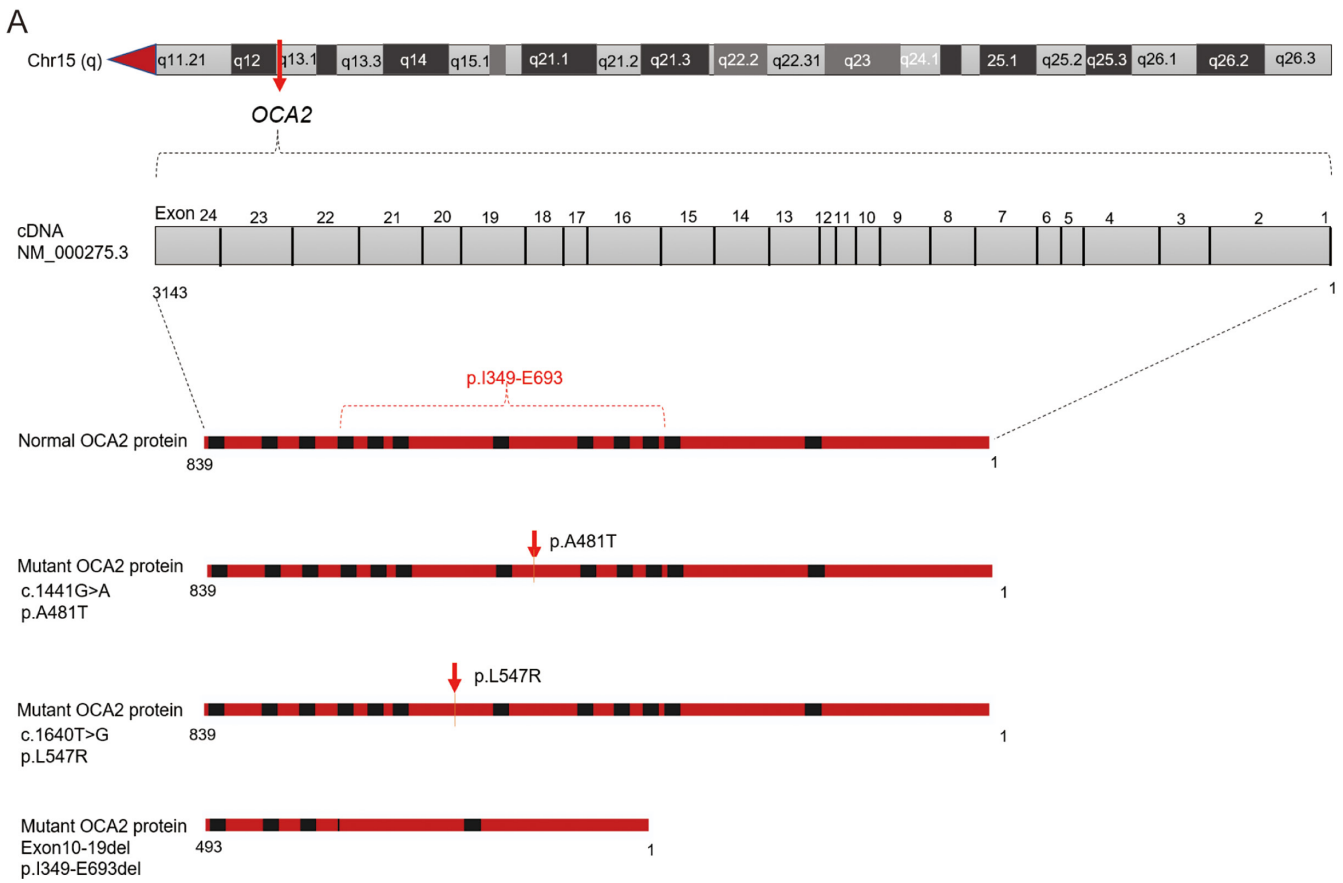

FIGURE 2 Variants pattern of the *OCA2* gene and protein. Red region represents topological domain, black region represents transmembrane domain. Arrows indicate the location of the mutations.

tools indicated that the variant c.1640T>G (p.L547R) was damaging (Table 1).

These two variants, c.1441G>A (p.A481T) and c.1640T>G (p.L547R), were found to be located within the topological domain (Figure 2). In addition, the deletion of exons 10-19 resulted in the loss of an amino acid sequence in the coding protein, leading to a shorter mutant protein and a reduction in the 3 to 9 transmembrane α-helices domains (Figure 2). Furthermore, an analysis of evolutionary conservation by multispecies alignment of the amino acids encoded by *OCA2* revealed that the variant c.1441G>A (p.A481T) caused a change from a highly conserved alanine to threonine (Figure 3a), while the variant c.1640T>G (p.L547R) caused a changer from a highly conserved leucine to arginine (Figure 3b).

In addition, as predicted by SWISS-MODEL, the amino acid changes caused by the variant c.1441G>A (p.A481T) resulted in alterations in hydrogen bonds (Figure 4a,b),

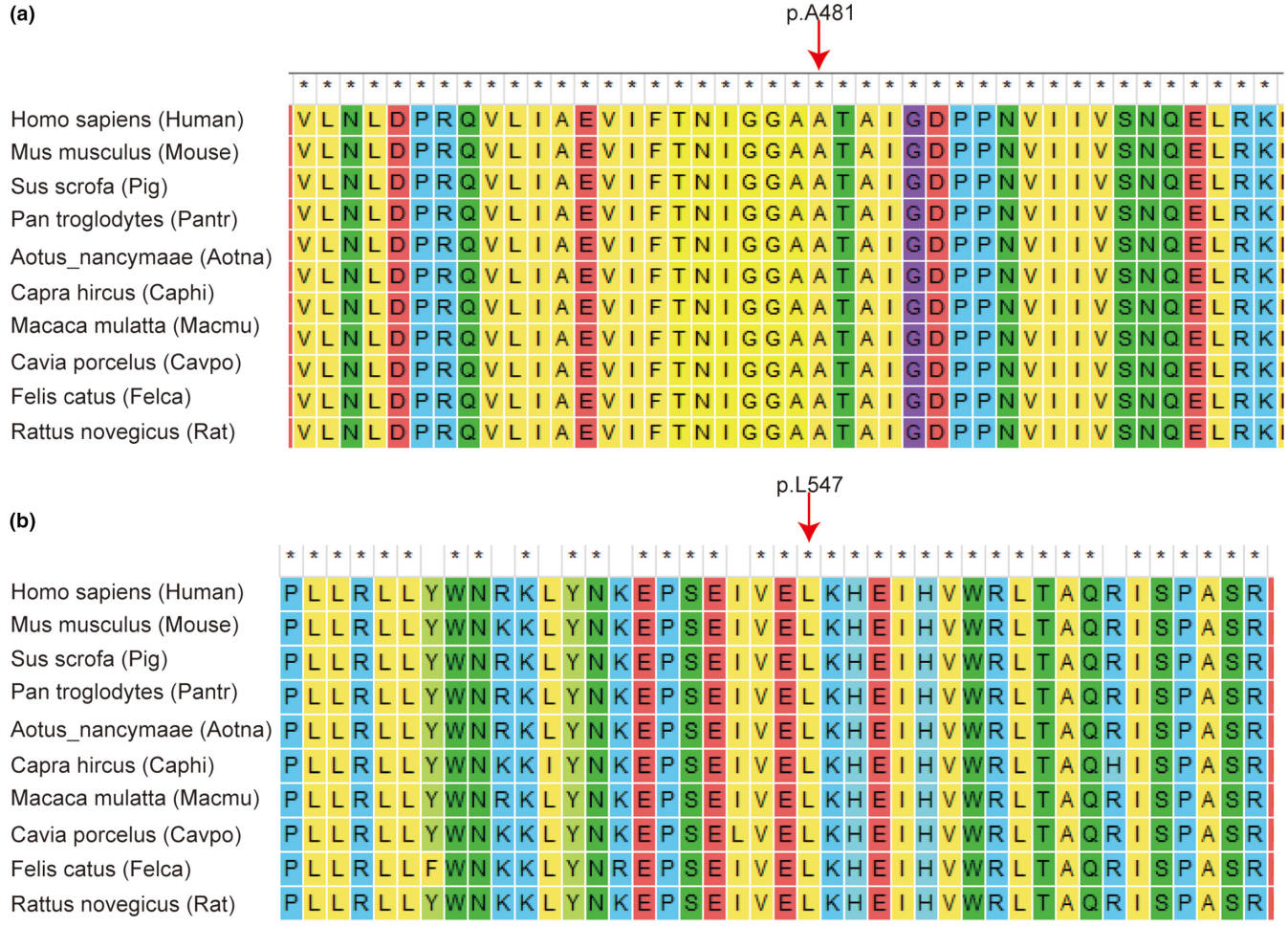

FIGURE 3 Evolutionary conservation analysis of the mutations in the *OCA2* gene. The p.A481 (a) and p.L547 (b) in the *OCA2* gene are highly conserved amino acids throughout evolution.

and the variant c.1640T>G (p.L547R) also caused changes in hydrogen bonds (Figure 4c,d). Furthermore, the deletion of exons 10-19 seriously affected the conformation of the OCA2 protein, leading to a non-functional truncated protein (Figure 4e). Overall, all three variants were found to have a damaging effect on the normal function of the OCA2 protein, suggesting that they may be the genetic etiology of the proband.

3.4 | PPI and functional annotation analysis

The PPI network analysis of *OCA2* by STRING revealed 11 nodes, 28 edges, and 10 genes (Figure 5a). The top proteins with higher degrees were *MC1R*, *PMEL*, *SLC24A5*, *SLC45A2*, *TYR*, and *TYRP1*, all having a degree of 6. The GO enrichment analysis then indicated that these genes interacted with *OCA2* in various biological processes such as melanin biosynthetic process, melanin metabolic process, and secondary metabolite biosynthetic process of BP. In terms of cellular component, the interaction was observed in Melanosome and pigment granule. Furthermore, the genes were found to be associated with monooxygenase activity and symporter activity of MF (Figure 5b). These findings highlight the crucial role of *OCA2* in melanin biosynthesis and metabolism.

3.5 | Follow-up

The proband carried the OCA2 compound heterozygous pathogenic variants, therefore, we provided genetic counseling and recommended genetic screening for his spouse before future pregnancies or prenatal diagnosis after pregnancy. Since the parents of the proband had no intention of having another child, genetic counseling was not necessary for them. However, the sister carried only a single variant, and the carrier status of her husband was unknown. Therefore, it was advised that her husband undergo genetic screening to confirm whether he carries a pathogenic variant of the *OCA2* gene.

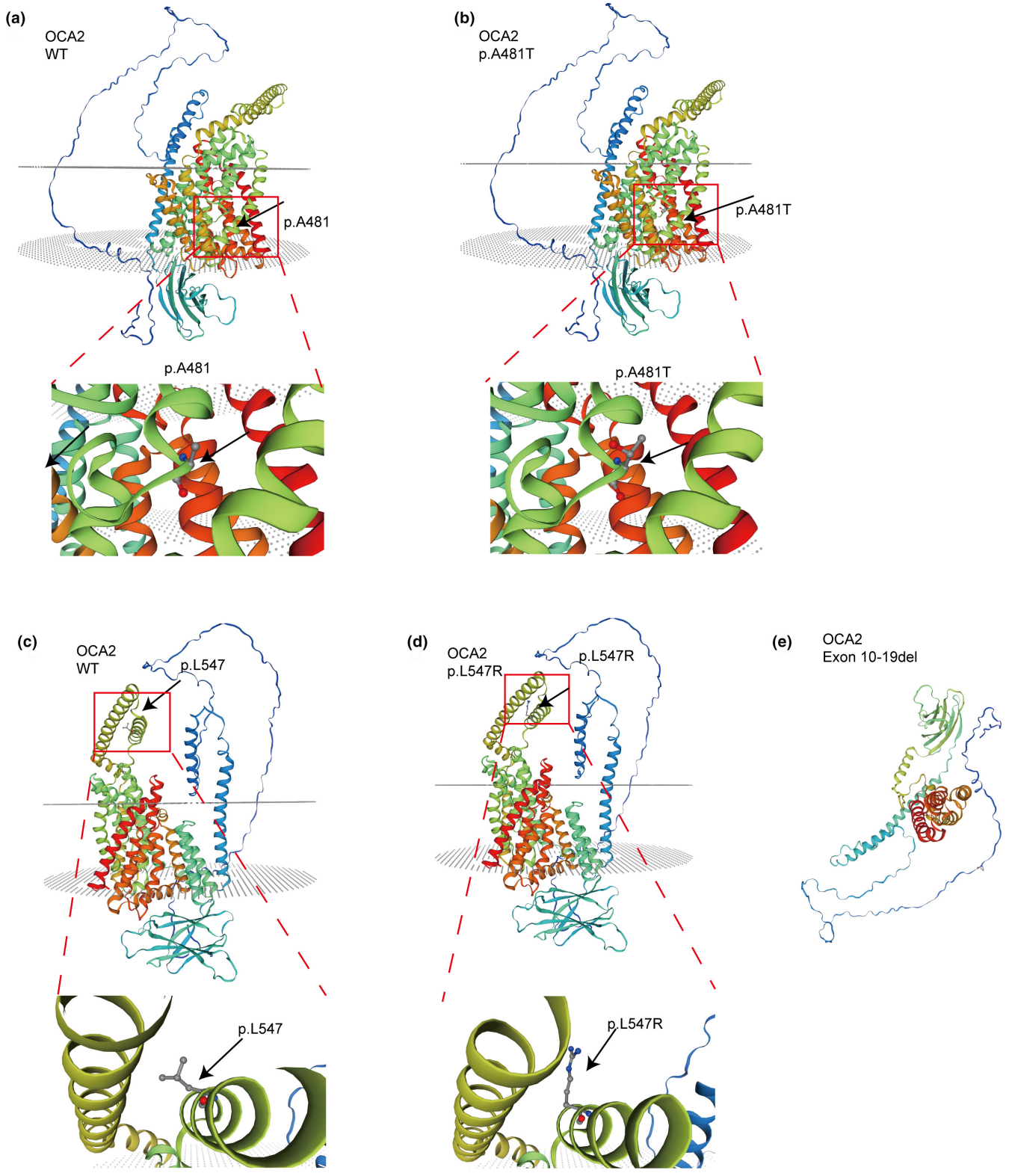

FIGURE 4 Modeling of wild-type and mutated OCA2 proteins by SWISS-MODEL. (a) and (C) The wild-type OCA2 protein. (b) p.A481T. (d) p.L547R. (e) Structural representation of exons 10–19 deletion.

Following genetic verification, it was determined that the fetus of the proband's sister did not carry the three variants of *OCA2*. The baby, a girl, was born at 36 gestational weeks and is in good health. These results are consistent with the findings of the prenatal diagnosis. This study further supports the efficacy of amniocentesis at 18+ weeks of pregnancy for genetic detection of postnatal diseases such as OCA.

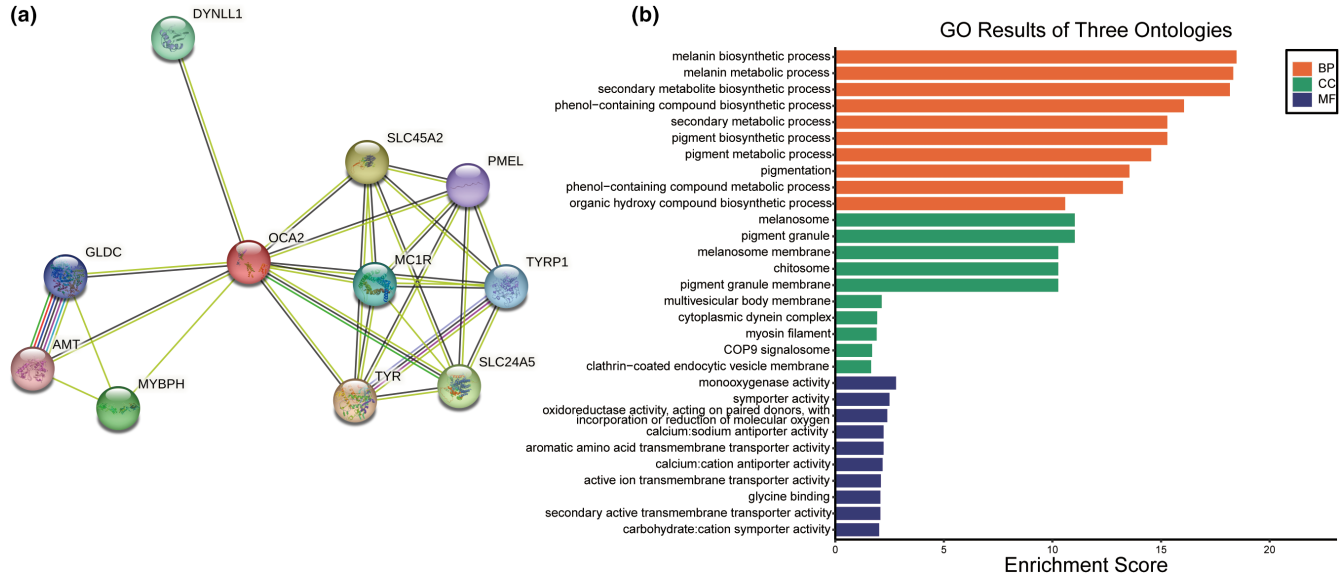

FIGURE 5 Go enrichment analysis of the PPI network of *OCA2*. (a) PPI network analysis of interacting genes with *OCA2* gene produced by STRING. Circles represent nodes, and lines represent edges. (b) GO enrichment analysis of target genes.

4 | DISCUSSION

The *OCA2* gene encodes a protein that consists of 12 transmembrane α-helical domains, which is an intact membrane protein belonging to the Na+/H+ antiporter family. The OCA2 protein is proposed to be an important component of melanosome-specific anion channels (Bellono et al., 2014). Dysregulation of OCA2 expression, one of the first genes associated with pigment decline, impacts the number of melanosomes. Specifically, decreased OCA2 expression leads to a decrease in the number of mature stage IV melanosomes, while the number of stage I and II melanosomes increases (Park et al., 2015). Furthermore, OCA2 has been found to regulate the pH in stage I and II melanosomes by controlling chlorine current, which is critically for tyrosinase activity and melanin production (Bellono et al., 2014; Le et al., 2020; Loftus et al., 2021). These studies collectively suggest that OCA2 primarily affects the transport of tyrosine, a precursor of melanin synthesis, and the pH of melanosomes, thereby contributing to disease occurrence (Bellono et al., 2014; Chen et al., 2002; Ni-Komatsu & Orlow, 2006).

A large number of *OCA2* gene variants have been identified, and 477 pathogenic/likely pathogenic variants have been included in the ClinVar database as of March 2023. Among these variants, the 2.7 kb deletion on exon 7 of the *OCA2* gene is the most common variant in Africans, African Americans, Haitians, and Congolese. This deletion causes a frame-shift mutation in the first luminal loop of the OCA2 protein, resulting in the production of a non-functional truncated protein (Mavinga et al., 2022; Stevens et al., 1997; Wang et al., 2017). Other extensively studied pathogenic variants in *OCA2* include p.V443I, p.P743L and p.A481T. Additionally, a variant with 22.4% frequency, c.1456G>T/p.Asp486Tyr, has been identified as one of the common variants of *OCA2* in the Pakistan region (Shakil et al., 2022). In Southwestern Chinese families with OCA type II, the most common variant is c.1255C>T (p.R419W) (Xiao et al., 2022). OCA type II is caused by homozygous or compound heterozygous variants in the *OCA2* gene, and patients with the homozygous form may exhibit a more severe phenotype than patients with complex heterozygous variants (Wang et al., 2015).

In the family affected by OCA, the present study identified three variants in the *OCA2* gene: p.A481T, p.L547R, and exons 10-19del, using WES and Sanger sequencing. It was found that the proband inherited the p.A481T and p.L547R variants from his father, and the exons 10-19del variant from his mother. The co-segregation of these variants in the *OCA2* gene was observed in this family. Previous reports have indicated that majority of missense variants in the *OCA2* gene are located in the loop between the transmembrane domains (Ma et al., 2021; Spritz, 1994). However, in the present study, both missense variants were found to occur in the P_permease domain. Previous studies have shown that the A481T variant leads to a reduction in the functional activity of the OCA2 protein in melanogenesis, to approximately 70% of the wild-type allele (Saitoh et al., 2000; Sviderskaya et al., 1997). In the case of our study, who is hemizygous, it is likely that he may only possess approximately 35% functional activity of the wild-type in melanin production. Suzuki et al. reported that all three patients with a mild phenotype had the A481T allele (Suzuki, Miyamura, Matsunaga,

et al., 2003). A comprehensive analysis of numerous cases revealed varying mutation spectra of the *OCA2* gene across different populations. Furthermore, even within a specific population, the results may vary depending on the number of cases studied. Yuasa et al. (2011) found that the A481T variant occurs widely in Northern Eurasia, with a varying frequency of the A allele ranging from 0.0% to 7.4% in Chinese Han, Japanese, and Korean populations, but not observed in European, South Asian and African samples. However, Kidd et al. (2020) reported that certain populations in Northern Europe, such as Chuvash and Vologda Russians, the A481T was present at a low frequency of 1%–3%, reaching 5%–7% in Finnish samples. Eaton et al. (2015) examined 419 East Asian individuals living in Canada and found that the frequency of the A allele was 3.3% and that the A481T variant was significantly correlated with the level of melanin in the samples. Furthermore, Ma et al. (2021) recently identified 28 Chinese families with OCA type II and found that A481T was the most common pathogenic variant in *OCA2*, with a frequency of 10.71% (6/56). Overall, these results suggest the different expressivity of *OCA2* gene in different genetic backgrounds. However, the pathogenicity of p.A481T has been subjected to Conflicting interpretations of pathogenicity (Likely pathogenic (1), Uncertain significance (4), Benign (4), Likely benign (2)) in the ClinVar database. According to Suzuki, Miyamura, et al. (2003), the A481T variant may be a non-pathogenic variant, but it may be associated with OCA type II in rare cases, such as in hemizygosity or when combined with a null mutant allele. Nevertheless, this variant was considered to be an Asian-specific hypochromic allele (Yuasa et al., 2007). Therefore, the p.A481T may be one of the causes of the reduced production of melanin observed in the patient in our study.

In the present study, we applied in-silico prediction to determine the harmfulness and effects on OCA2 protein function of two novel pathogenic variants. The missense mutation c.1640T>G (p.L547R), a previously unreported variant, was found to be evolutionarily conserved and predicted to cause changes in hydrogen bonds due to the substitution of leucine with arginine. This substitution occurs at the p.L547 residue in the seventh topological domain of the OCA2 protein, and even a small perturbation in this region could result in the inactivity of the protein. Various algorithms used to assess the effect of variation on protein function predicted that p.L547R would be deleterious (Table 1). Another variant studied was the deletion of exons 10-19, which has not been previously reported and covers the 3rd to 9th transmembrane domains (Figure 2). This deletion leads to the partial loss of the P-permease domain, resulting in the production of a truncated non-functional protein. Previous research has indicated that significant deletions in this region of the *OCA2* gene are genetic causes of patients with OCA type II. For instance, the exons 17-21 deletion of the *OCA2* gene was identified in an 11-month-old boy with non-syndromic OCA (Wang et al., 2019), and deletions in exons 3–20, exons 3–14, exons 7–8, exons 20–24, and exons 22–24 of the *OCA2* gene have been observed in patients with OCA type II (Rooryck et al., 2008; Shahzad et al., 2017). Thus, these two variants in the *OCA2* gene were found to be the genetic causes underlying the patient's condition in this study, highlighting the crucial role of WES in copy number analysis for genetic diagnosis.

5 | CONCLUSION

In summary, we performed accurate genetic diagnosis of a male proband with OCA using WES analysis and found two missense variants c.1441G>A (p.A481T) and c.1640T>G (p.L547R) in the *OCA2* gene. Additionally, one gross deletion (exons 10–19) was also identified. Notably, the c.1640T>G (p.L547R) variant and the exons 10–19 deletion variants were novel variants that had not been previously reported. These findings significantly contribute to the mutational spectra of the *OCA2* gene. Overall, our study highlights the utility of WES as a valuable tool in accurately diagnosing albinism, thereby facilitating genetic counseling for the disease.

AUTHOR CONTRIBUTIONS

Beilei Jiang, Quan Liu: Study concepts. Beilei Jiang, Hua Zhang, Quan Liu: Study design and data acquisition. Yuling Kan: Clinical information collection. Yuling Kan, Xueping Gao, Zhaoli Du: Data analysis/interpretation. Beilei Jiang, Hua Zhang, Yuling Kan, Xueping Gao: Manuscript preparation. Quan Liu: Manuscript editing.

ACKNOWLEDGMENTS

Not applicable.

CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Hefei First People's Hospital.

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SUPPORTING INFORMATION

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