Identification of *TYR* Whole Gene Deletion in a Patient with Oculocutaneous Albinism by Next Generation Sequencing

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Abstract

Oculocutaneous albinism (OCA) comprises a group of genetically heterogeneous, autosomal recessive disorders characterized by a partial or complete absence of melanin pigmentation in the skin, hair, and eyes, associated with visual impairment. In this study, we analyzed several genes in an Iranian male infant affected by OCA. Clinical investigations and laboratory evaluations were performed for the proband. A pedigree chart was also drawn. Genomic DNA was extracted from the proband and both parents. A targeted gene panel was sequenced by next-generation sequencing to identify pathogenetic variants. A deletion of exons 1–5 in the *TYR* gene was confirmed in the proband. Logically, the parents should be heterozygous for this mutation. The results of this research demonstrate the efficiency of targeted high-throughput sequencing in diagnosing heterogeneous disorders like OCA and detecting large genomic rearrangements. This deletion mutation may have resulted from an unequal crossing-over event in an ancestral lineage.

Keywords Oculocutaneous albinism (OCA), *TYR* gene deletion, Next-generation sequencing (NGS)

Introduction

Oculocutaneous albinism (OCA) comprises a group of rare genetically heterogeneous disorders caused by defects in the melanin biosynthesis pathway, resulting in complete or partial loss of pigmentation in the skin, hair, and eyes (1). Optic system abnormalities, such as nystagmus, photophobia, iris translucency, foveal hypoplasia, strabismus, retinal hypopigmentation, and decreased visual acuity are also observed in affected individuals (2,3). The incidence of OCA ranges from 1 in 10,000 to 20,000 in newborns across different ethnic populations. This indicates that approximately 1 in 70 people carries an OCA-related gene mutation (3,4)(Table 1).

OCA is an autosomal recessive genetic disorder classified into a non-syndromic form, caused by mutations in several genes such as *TYR, TYRP1, OCA2, SLC45A2, SLC24A5, SLC24A4* genes, and a syndromic form, which results from defects in various genes including *AP3B1, HPS1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, PLDN, LYST, MYO5A, RAB27A*, and *MLPH* genes (5,6). Additionally, mutations in GPR143 are the only known and major cause of X-linked ocular albinism (6–8).

Defects in the *TYR* gene cause OCA1, the most prevalent subtype of the disorder among Caucasian populations, representing approximately 50% of reported cases (9–11). The *TYR* gene spans more than 50 kb of genomic DNA on chromosome 11q14.3, consisting of five exons and encoding a 529 amino-acid protein (12,13). A tyrosinase-related gene (tyrosinase-like gene) exists on chromosome 11q, containing only exons 4 and 5, and shares 98.5% homology with the *TYR* gene (14,15). Tyrosinase catalyzes essential steps in the melanin biosynthesis pathway, including the conversion of tyrosine to dopaquinone (16,17).

OCA1 is clinically classified into two forms: OCA1A, the most affected subtype, results from a total lack of *TYR* activity, whereas OCA1B is characterized by residual enzyme activity (18). It is impossible to accurately distinguish OCA subtypes based solely on clinical features. Therefore, molecular analysis is important for precise diagnosis and effective genetic counseling. Here, we report a patient affected by OCA. Targeted enrichment and next-generation sequencing (NGS) of 14 genes were performed to discover the causative mutation in this family.

Material and Methods

Subject and Clinical evaluations:

A two-month-old boy was referred to Emam Hossein Children's Hopital. The patient was the only child of a consanguineous Iranian parents, related as first cousins. He was delivered following an uneventful gestation and normal hospital birth. At birth, a weight of 4.2 kg was recorded, with a head circumference of 39 cm and a length of 51 cm. Gray-blue irises, nystagmus and generalized hypopigmentation of the hair, eyelashes, eyebrows, and skin were observed. Additionally, facial abnormalities were noted. However, ophthalmologic evaluation and examination of internal organs revealed no abnormalities. His mental development was normal. A family history assessment showed no similar phenotype among any first-degree or second-degree relatives (Figure 1). High-performance liquid chromatography (HPLC) amino acid analysis was performed, and all results were within the normal range.

Ethical approval:

This study was approved by the ethics community of Isfahan University of Medical Science (2400173). Informed consent was obtained from the parents in accordance with ethics guidelines.

Next generation sequencing experiments:

Informed consent was obtained from the parents in accordance with the ethics committee guidelines of (Isfahan University of Medical Sciences). Genomic DNA was extracted from peripheral blood using the standard salting-out method (19,20). Genetic sequencing was carried out using a custom-designed NimbleGen capture chip targeting the genes of *TYR, OCA2, TYRP1, SLC45A2, AP3B1, HPS1, HPS3, HPS4, HPS5, HPS6, DTNBP1 and BLOC1S3* (20). Targeted next-generation sequencing was subsequently performed on an Illumina platform (San Diego, CA) at BGI Clinical Laboratories. The sequencing platform covered more than 95% of the target regions with a sensitivity of exceeding 99%. Deletions, duplications, point mutations and micro-insertions (<20 bp) were simultaneously detected using tools provided by Thermo Fisher Scientific Inc. (USA).

Results

NGS data analysis revealed sixteen DNA variants in seven genes, one of which was identified as pathogenic (*TYR*). Three homozygous and two heterozygous variants were found in the *OCA2* gene. Four homozygous variants were found within *HPS4*. Both *AP3B1* and *HPS5* had two homozygous variants each. Heterozygous variants were observed in the *HPS1* and *HPS3* genes. Seven synonymous variants, six nonsynonymous variants, and two intronic variants were found (17). The observation of the BAM files through the IGV software showed that the proband was homozygous for the exon 1–5 deletion mutation of the *TYR* gene. According to HGVS nomenclature (21), this variant is designated as NM_000372.5(TYR):c.(1-5)del at the cDNA level. This deletion is expected to disrupt the entire coding sequence of *TYR*, leading to an entire loss of tyrosinase function and fulfills the criteria American college of medical genetics guideline for being categorized as pathogenic.

Discussion

Oculocutaneous albinism (OCA) exists in two forms: syndromic and non-syndromic, and it is a genetically heterogeneous disorder (Table 1). In this study, we presented a case of albinism with facial anomalies and identified the mutation using targeted-enrichment high-throughput sequencing. The results demonstrate the high efficiency of this technique in the molecular analysis of heterogeneous disorders and large genomic aberrations (17). In contrast to African and African-American populations, where *OCA2* is the most common cause of albinism (1,15,22), about 60% of Iranian patients have a homozygous or compound heterozygous mutation within *TYR*, in agreement with the Caucasian population (23,24).

Surprisingly, despite being a rare inherited disease and the elevated prevalence of consanguineous marriages in Iran (25), it most often occurs in such families without previous history, as stated by Khordadpoor-Deilamani et al (24), and mentioned in this report.

Approximately 500 causative mutations have been documented in the Human Gene Mutation Database (HGMD(26)). These mutations are all associated with the single *TYR* gene located on chromosome11q14.3 (13). While most mutations found within *TYR* are missense mutations, a few small insertions and deletions have been reported (27)(Figure 2). Gross deletions are a rare cause of disease. Therefore, we aimed to gather data on some pathogenic or likely pathogenic deletions in *TYR* and their associated Phenotype (28)(

Table 2).

Whole gene deletions have been previously reported in compound heterozygous states, and the patients had the OCA1B phenotype (10,29). Due to the large deletion, verifying the mutation via Sanger sequencing was not a simple task (15). however, employing a quantitative method such as MLPA, array CGH, or quantitative real-time PCR could be considered to assess gene dosage (20).

To our current understanding, this is the first report of a truly homozygous state of This deletion mutation and the first report of whole gene deletion in Iran. As a hypothesis, the mutation may have resulted from unequal crossing over between the gene and its pseudogene on chromosome 11q, which leads to gene deletion. Due to consanguineous marriages, it seems that the mutation has been inherited from a common ancestor.

Conclusion

The results support clinical diagnosis. The phenotypes of the infant and the molecular findings suggest OCA1A. We expect that identifying the mutant gene will significantly improve genetic counseling for the pedigree and assist in future pregnancies. Therefore, the parents and other family members should consider genetic counseling and testing.

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Data availability the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of Interest the authors declare no conflict of interest.

Informed consent Written informed consent was obtained from all participants in the study and written consent to participate was obtained from the parents of the patient (younger than the age of 16). Written informed consent for publication of clinical details and images was also obtained from all participants and from the parents of participants under the age of 18.

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Figures

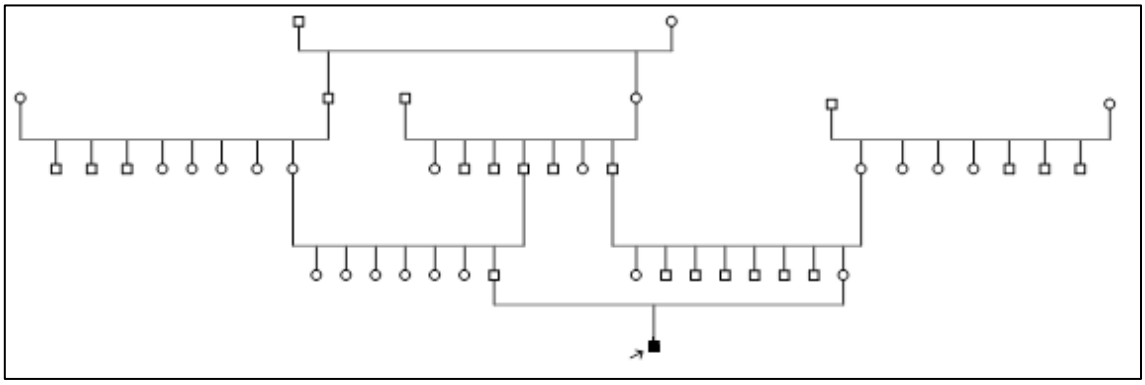

Figure 1. Family pedigree. An infant boy affected by OCA1A resulted from a consanguineous marriage. There is no family history of the disease.

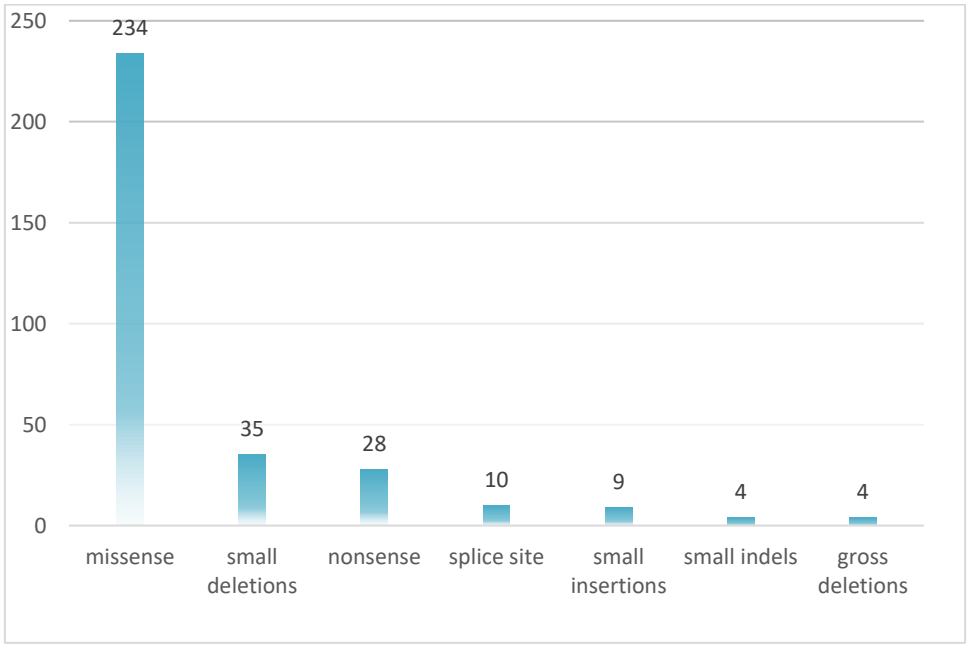

Figure 2. Prevalence of different types of *TYR* mutations. According to human gene mutation database (HGMD) missense mutations are the most common types of mutations found within *TYR*. Small deletion mutations stand at the second place and after that nonsense, splice site and small insertions have the major role respectively. Small indels and gross deletions are not very common in the pathogenesis of the disease.

Table 1 . A List of genes involved in OCA.

	Symbol	Description	Category	Reference
1	*TYR*	*Tyrosinase*	*Protein Coding*	(30,31)
2	*SLC24A5*	Solute Carrier Family 24 Member 5	Protein Coding	(30,31)
3	*SLC45A2*	*Solute Carrier Family 45 Member 2*	*Protein Coding*	(30,31)
4	*TYRP1*	Tyrosinase Related Protein 1	Protein Coding	(30,31)
5	*LRMDA*	*Leucine Rich Melanocyte Differentiation Associated*	*Protein Coding*	(30,31)
6	*DCT*	Dopachrome Tautomerase	Protein Coding	(30,31)
7	*HPS6*	*HPS6 Biogenesis Of Lysosomal Organelles Complex 2 Subunit 3*	*Protein Coding*	(30,31)
8	*HPS4*	HPS4 Biogenesis Of Lysosomal Organelles Complex 3 Subunit 2	Protein Coding	(30,31)
9	*HPS3*	*HPS3 Biogenesis Of Lysosomal Organelles Complex 2 Subunit 1*	*Protein Coding*	(30,31)
10	*MC1R*	Melanocortin 1 Receptor	Protein Coding	(30,31)
11	*HPS1*	*HPS1 Biogenesis of Lysosomal Organelles Complex 3 Subunit 1*	*Protein Coding*	(30,31)
12	*HPS5*	*HPS5 Biogenesis Of Lysosomal Organelles*	*Protein Coding*	(30,31)
13	*GPR143*	G Protein-Coupled Receptor 143	Protein Coding	(30,31)
14	*BLOC1S6*	*Biogenesis Of Lysosomal Organelles Complex 1 Subunit 6*	*Protein Coding*	(30,31)
15	*DTNBP1*	Dystrobrevin Binding Protein 1	Protein Coding	(30,31)
16	*LRMDA*	*Leucine-Rich Melanocyte Differentiation-associated protein; LRMDA*	*Protein Coding*	(30,31)
17	*AP3B1*	Adaptor-Related Protein complex 3, Beta-1 Subunit; AP3B1	Protein Coding	(30,31)
18	*MLPH*	*Synaptotagmin-Like Protein lacking C2 Domains A; SLAC2A.*	*Protein Coding*	(30,31)

Table 2. Overview of *TYR* Gene deletions (28).

Variation	Condition	Classification
NM_000372.5(TYR): c.25del)	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.69del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.178_179del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic/Likely pathogenic*
NM_000372.5(TYR):c.216del	*Tyrosinase-negative oculocutaneous albinism*	*Pathogenic*
NM_000372.5(TYR):c.221_222del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.404_621del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.422del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Likely pathogenic*
NM_000372.5(TYR):c.466_447del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.549del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Likely pathogenic*
NM_000372.5(TYR):c.572del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.573del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.580del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.649del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.692_696del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Likely pathogenic*
NM_000372.5(TYR):c.696del	*not provided*	*Pathogenic/Likely pathogenic*
NM_000372.5(TYR):c.781_784del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.787_790del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.820_3del	*Tyrosinase-negative oculocutaneous albinism*	*Likely pathogenic*
NM_000372.5(TYR):c.825_828del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.841del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.911_914del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.943_948del	*nonsyndromic Oculocutaneous Albinism*	*Likely pathogenic*
NM_000372.5(TYR):c.1037-10 1041del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.1059del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Likely pathogenic*
NM_000372.5(TYR):c.1141_1160del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.1164del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.1177del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Pathogenic*
NM_000372.5(TYR):c.1214del	*Skin/Hair/Eye pigmentation 3, Light/Dark Skin*	*Likely pathogenic*
NM_000372.5(TYR):c.1237del	*not provided*	*Pathogenic*
NM_000372.5(TYR):c.1267del	*Tyrosinase-negative oculocutaneous albinism*	*Pathogenic*
NM_000372.5(TYR):c.1322del	*Tyrosinase-negative oculocutaneous albinism*	*Pathogenic*

Identification of *TYR* Whole Gene Deletion in a Patient with Oculocutaneous Albinism by Next Generation Sequencing

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شناسایی حذف کامل ژن *TYR* در یک بیمار مبتلا به آلبینیسم چشمی_پوستی با استفاده از توالی‌یابی نسل جدید

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چکیده

آلبینیسم چشم–پوستی (OCA) یک اختلال اتوزوم مغلوب ژنتیکی با هتروژنیسی بالا است که با کاهش یا عدم وجود کامل رنگ‌دانه در مو، پوست و چشم‌ها مشخص می‌شود و با اختلالات بینایی همراه است. در این مطالعه ، چندین ژن در یک نوزاد پسر ایرانی مبتلا به OCA مورد بررسی قرار گرفت. ارزیابی‌های بالینی و آزمایشگاهی برای فرد مبتلا انجام شد و نمودار شجره نیز ترسیم گردید. DNA ژنومی از فرد مبتلا و والدین او استخراج شد. آنالیز جهش با استفاده از فناوری توالی‌یابی نسل جدید بر روی مجموعه‌ای از ژن‌ها انجام گرفت. حذف اگزون‌های ۱ تا ۵ در ژن *TYR* در فرد مبتلا شناسایی شد. منطقی است که والدین به‌صورت هتروزیگوت حامل این جهش باشند. نتایج این مطالعه نشان‌دهنده کارایی توالی‌یابی هدفمند با توان بالا در تشخیص بیماری‌های هتروژن مانند OCA و شناسایی بازآرایی‌های بزرگ ژنومی است. این جهش حذف ممکن است ناشی از کراسینگ اور نابرابر در یکی از تبارهای اجدادی باشد.

واژه‌های کلیدی : آلبینیسم چشمی–پوستی (OCA)، حذف ژن *TYR*، توالی‌یابی نسل جدید (NGS)