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CONCISE COMMUNICATION

# Identification of two Chinese oculocutaneous albinism type 6 patients and mutation updates of the *SLC24A5* gene

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## ABSTRACT

**Oculocutaneous albinism (OCA) is a rare and heterogeneous disorder characterized by hypopigmentation of the skin, hair and eyes. Thirty OCA type 6 (OCA6) patients with 24 mutations in *SLC24A5* have been reported across various populations; however, only one patient has been identified in a Chinese population. This study identifies two novel *SLC24A5* frame-shift variants in two unrelated Chinese patients and both are predicted to be pathogenic by American College of Medical Genetics guidelines. The genotypes and phenotypes of all three Chinese OCA6 patients are unique compared with those identified in other populations. All of the mutations identified to date in Chinese OCA6 patients are predicted to be non-functional, a finding that is useful in guiding genetic diagnosis and counseling for OCA6 in China.**

**Key words:** **oculocutaneous albinism type 6, *SLC24A5*, genotyping, mutation, next-generation sequencing.**

## INTRODUCTION

Oculocutaneous albinism (OCA) is a group of rare and heterogeneous autosomal recessive disorders caused by deficiencies of melanin in the skin, hair and eyes, and is often accompanied by poor vision, strabismus, nystagmus and photophobia. Six non-syndromic OCA genes (*TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *SLC24A5*, *LRMDA*) are reported to cause OCA types 1–4, OCA6 and OCA7, respectively.[1]

We first reported on a clinically diagnosed Chinese OCA patient with recessive mutations in *SLC24A5* and identified more immature than mature melanosomes in the patient's epidermal melanocytes. This was designated as OCA6, a new subtype of OCA.[2] To date, 30 OCA6 patients with 24 *SLC24A5* mutations have been reported in different populations.[1–7] However, in the Chinese population, no additional cases of OCA6 have been reported since the initial case study, suggesting that OCA6 is a rare form of OCA. In this study, we describe two unreported OCA6 patients with two novel homozygous mutations in *SLC24A5*.

## CASE REPORT

All OCA patients were from different Chinese provinces and next-generation sequencing was performed on all.[8]

Two patients were clinically diagnosed as non-syndromic OCA. No consanguineous marriages were claimed by their parents. Molecular testing in patients 1 and 2 revealed two homozygous frame-shift alleles: c.500dupT (p.S168Ifs*15) and c.498_499delAC (p.L167Ifs*15), respectively. According to American College of Medical Genetics standards,[9] both are predicted to be pathogenic alleles.

The clinical and genetic features of the three Chinese OCA6 patients are shown in Table 1 and Figure 1. The clinical features and genotyping results for patient 3 have been reported previously.[2]

## DISCUSSION

*SLC24A5* is located on chromosome 15q21.1. It encodes the NCKX5 protein (solute carrier family 24 [sodium/potassium/calcium exchanger], member 5), a potassium-dependent exchanger that is required for melanosome maturation and for pigment production in mature melanosomes.[2] The mutant proteins found in some OCA6 patients[2,5] did not rescue the pigment production when transfected in NCKX5 knockdown melanocytes.[10] Furthermore, the authors found that mitochondrial NCKX5 transfers calcium into melanosome for its maturation and pigment production,[10] revealing the underlying mechanism of OCA6.

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**Table 1.** Clinical and genetic findings of the three oculocutaneous albinism type 6 patients

| | Clinical manifestations | | | | | | Genetic variants | |
|---|---|---|---|---|---|---|---|---|
| No. | Age/sex | Skin | Hair | Iris | Visual Acuity | Foveal hypoplasia | Paternal mutations | Maternal mutations |
| 1 | 8 months/F | Fair | Blond | Brownish | Reduced | Yes | c.500dupT† (p.S168Ifs†) | c.500dupT† (p.S168Ifs†) |
| 2 | 18 months/F | Fair | Light blond | Blue | Reduced | Not available | c.498_499delAC† (p.L167Ifs†) | c.498_499delAC† (p.L167Ifs†) |
| 3 | 3 years/F | Fair | Light brown | Brownish | 40/200R, 40/200L | Yes | c.1361insT (p.L454Ffs†) | c.591G>A (p.W197X) |

†Previously unknown alleles.

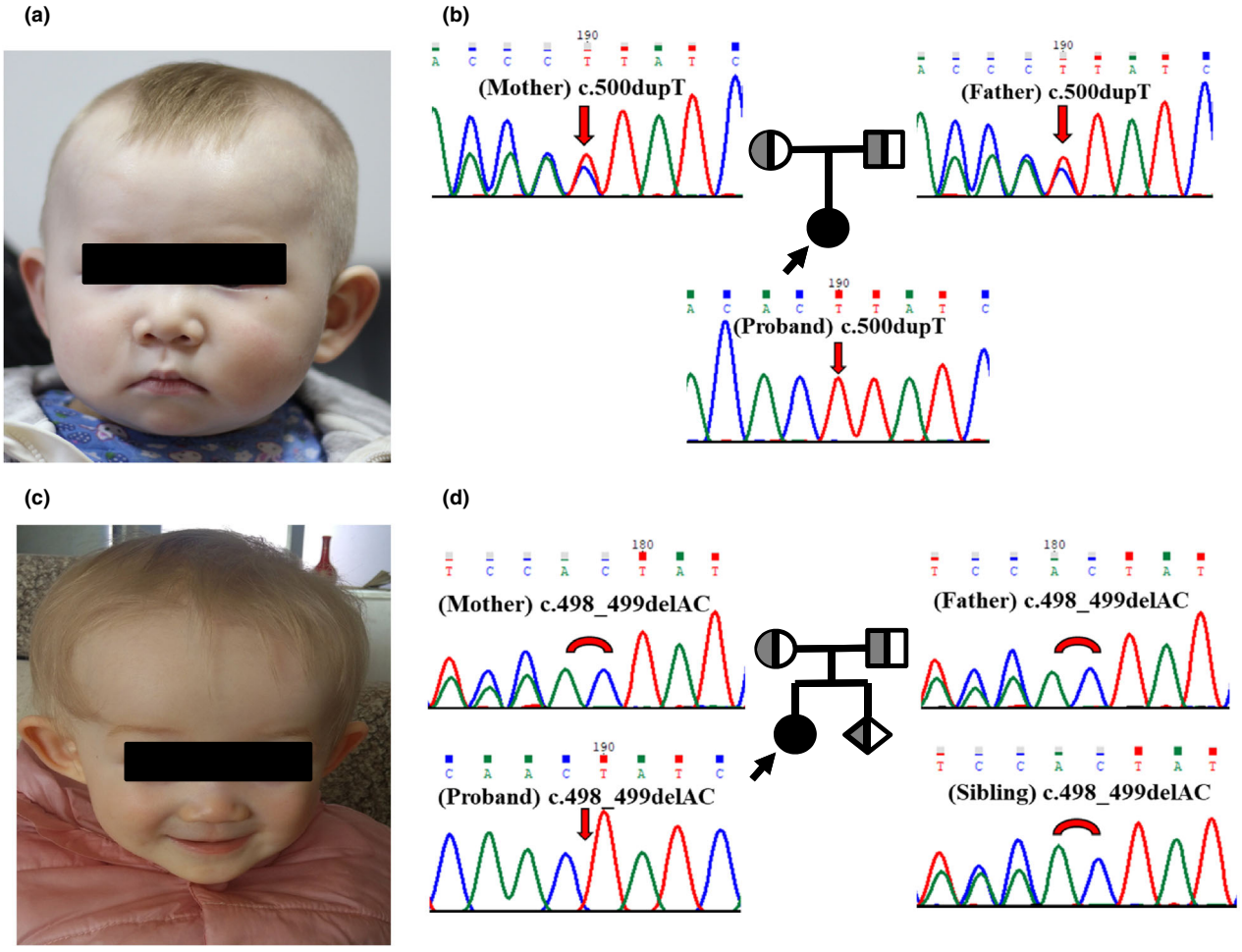


**Figure 1.** Clinical features and mutational alleles of the two previously unreported oculocutaneous albinism type 6 patients. (a) Patient 1 with fair skin, blond hair and brownish iris. (b) The patient inherited the homozygous mutation c.500dupT in *SLC24A5* from her parents. (c) Patient 2 with fair skin, light blond hair and blue iris. (d) The patient inherited the homozygous mutation c.498_499delAC in *SLC24A5* from her parents. The unborn sibling of patient 2 inherited the heterozygous mutation c.498_499delAC in *SLC24A5*.

Thirty OCA6 patients have been reported across various populations worldwide, including European, African and Asian people. Only three Chinese patients have been reported to date, which suggests a lower prevalence of OCA6 in China. Twenty-four mutations in *SLC24A5* are listed to cause OCA6 in the Human Gene Mutation Database and here we report two

**Table 2.** Twenty-six mutations in *SLC24A5*

| Type | Mutation alleles | Location | Race | References |
|---|---|---|---|---|
| Missense (7) | c.344C>A (p.A115E) | Exon 2 | French | Morice-Picard *et al*. (2014)[8] |
| | c.431G>T (p.G144V) | Exon 4 | Turkey | Lasseaux *et al*. (2018)[5] |
| | c.500T>C (p.L167P) | Exon 5 | Not Available | Lasseaux *et al*. (2018)[5] |
| | c.521G>A (p.R174K) | Exon 5 | French Guiana | Bertolotti *et al*. (2015)[4] |
| | c.546T>A (p.S182R) | Exon 5 | Syrian | Morice-Picard *et al*. (2014)[8] |
| | c.1096C>A (p.P366T) | Exon 8 | Caucasian | Lasseaux *et al*. (2018)[5] |
| | c.1202C>T (p.S401F) | Exon 9 | Morocco | Lasseaux *et al*. (2018)[5] |
| Nonsense (6) | c.184C>T (p.Q62*) | Exon 2 | French | Lasseaux *et al*. (2018)[5] |
| | c.216T>A/G (p.Y72*) | Exon 2 | Belgian/Italian | Morice-Picard *et al*. (2014)[8] Veniani *et al*. (2016)[9] |
| | c.591G>A (p.W197*) | Exon 5 | Chinese | Wei *et al*. (2013)[6] |
| | c.594T>A (p.Y198*) | Exon 6 | Caucasian | Lasseaux *et al*. (2018)[5] |
| | c.989G>A (p.W330*) | Exon 7 | French | Morice-Picard *et al*. (2014)[8] |
| | c.1361T>A (p.L454*) | Exon 9 | Caucasian/? | Lasseaux *et al*. (2018)[5] Lee *et al*. (2018)[10] |
| Splicing (2) | c.385+2T>G | Intron 3 | Italian | Veniani *et al*. (2016)[9] |
| | c.590+4A>G | Intron 5 | French/Algeria | Morice-Picard *et al*. (2014)[8] |
| Small deletions (7) | c.20_29del10 (p.Q7Rfs*61) | Exon 1 | Kosovo | Lasseaux *et al*. (2018)[5] |
| | c.32_33delGA (p.R11Kfs*32) | Exon 1 | Kosovo | Lasseaux *et al*. (2018)[5] |
| | c.641delT (p.L214Afs*12) | Exon 6 | Portuguese | Morice-Picard *et al*. (2014)[8] |
| | c.644_645delGT (p.C215Ffs*2) | Exon 6 | French | Lasseaux *et al*. (2018)[5] |
| | c.840_841delAA (p.I280Mfs*6) | Exon 6 | Caucasian | Lasseaux *et al*. (2018)[5] |
| | c.911_916delAAAGAA (p.K304_R305del) | Exon 7 | Tukey | Lasseaux *et al*. (2018)[5] |
| | c.498_499delAC (p.L167Ifs*15) | Exon 5 | Chinese | This study |
| Small insertions (3) | c.571_572insTAAT (p.Y191Lfs*2) | Exon 5 | Indian | Mondal *et al*. (2012)[7] |
| | c.1361dupT (p.L454Ffs*31) | Exon 9 | Chinese | Wei *et al*. (2013)[6] |
| | c.500dupT (p.S168Ifs*15) | Exon 5 | Chinese | This study |
| Gross deletions (1) | Exons 6–9 | Exons 6–9 | North African | Lasseaux *et al*. (2018)[5] |

additional novel mutations (c.500dupT and c.498_499delAC), shown in Tables 1 and 2. Notably, a small insertion, c.571_572insATTA, identified in an Indian patient did not result in ocular defects, suggesting it is a variant form of OCA6.[4] The splicing mutation (c.590+4A>G) has been detected in three unrelated OCA6 patients and the nonsense mutation (c.216T>A/G) has been detected in another three unrelated patients.[3,5,6] These may represent high-frequency *SLC24A5* mutations. Most OCA6 patients present with typical optic defects. However, skin, hair and iris colors varied among the patients presented here. In previous reports, hair color presentation varied from white to dark, with the blond/light brown color being the most common. Skin color ranged from unpigmented to pigmented and the most common color was fair/pale, whereas iris color ranged from light to dark brown and was most frequently blue, green or gray.[1,3,5,6] Our three Chinese OCA6 patients exhibited fair skin with light blond to light brown hair, which is very close to that of the majority of patients from other races but without the manifestations of either extreme light or dark color. In contrast, the iris colors in our patients were generally brownish or blue, which differs from those of other populations. The genotypes of these OCA6 patients and their racial background could explain the color variations. An index of more patients is required to reach any conclusion.

In summary, we report two additional Chinese OCA6 patients and two novel pathogenic mutations in *SLC24A5*, which expands the spectrum of the phenotypes and genotypes of OCA6 in Asian populations. These findings are useful for the genetic diagnosis and counseling of patients with OCA6.

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**CONFLICT OF INTEREST:** None declared.

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