



Oculocutaneous Albinism Type 7 with Recurrent Infections: A Case Report

Mehmet KILIÇ¹ , Mehmet Hazar ÖZCAN² , Erdal TASKIN³ , Hakan YILDIRIM⁴ , Aşkın ŞEN⁵ 

¹ Department of Pediatrics, Division of Allergy and Immunology, Firat University, School of Medicine, Elazig, Turkey

² Department of Pediatrics, Firat University, School of Medicine, Elazig, Turkey

³ Department of Pediatrics, Division of Neonatology, Firat University, School of Medicine, Elazig, Turkey

⁴ Department of Ophthalmology, Firat University, School of Medicine, Elazig, Turkey

⁵ Department of Medical Genetics, Firat University, School of Medicine, Elazig, Turkey

Corresponding Author: Mehmet Kılıç ✉ drmkilic@gmail.com

ABSTRACT

Oculocutaneous albinism (OCA) is a disorder of melanin biosynthesis characterized by hypopigmentation of the skin, hair, and retinal pigment epithelium. We present the clinical and laboratory features of two siblings, born to consanguineous Turkish parents, who were diagnosed with autosomal recessive OCA type 7. We detected a homozygous mutation in the *C10ORF11* gene (p.A23Rfs * 39) in both patients. Interestingly, the medical history revealed that both patients had suffered from recurrent respiratory tract infections since birth. The patients were investigated for suspected immunodeficiency and the results of the immune screening assays were normal. We believe these patients are noteworthy to report since presentation with infections has not been described in the prior descriptions of OCA type 7. As of this current writing, infectious problems have stopped in one of our cases since the age of five and a half years.

Keywords: Oculocutaneous albinism type 7, recurrent infection, immune system, genetic analysis, *C10ORF11* gene

INTRODUCTION

Oculocutaneous albinism (OCA) is an autosomal recessive inherited disorder of melanin biosynthesis in the melanocytes, characterized by a general reduction in the pigmentation of the hair, skin, and eyes. Seven types of OCA subtypes have been identified so far (OCA types 1 -7), four of which are well characterized (OCA types 1-4). Oculocutaneous type 2 albinism is the most frequent subtype. Oculocutaneous albinism has a worldwide prevalence of 1: 17,000 to 1: 20,000. However, the prevalence of subtypes in different ethnic populations varies greatly, also influenced by fertility rates and inbreeding (1,2). Symptoms such as congenital nystagmus, photophobia, hypopigmentation of the iris and retinal epithelium, foveal hypoplasia, refractive errors, decreased visual acuity, and sometimes impaired color vision can be seen in all types of oculocutaneous albinism (2,3).

Oculocutaneous albinism type 7 (OCA type 7) was formerly called OCA type 5. It is a rare autosomal recessive disease. Its prevalence is unknown. However, its prevalence worldwide is estimated to be <1 / 1000,000. A homozygous mutation in the gene *C10ARG11* (LRMDA; Leucine-Rich Melanocyte Differentiation Associated; 10q22.3) results in OCA type 7. The *C10ORF11* gene plays a role in melanocyte differentiation. The *C10ORF11* gene encodes a 198 amino acid protein containing three leucine-rich repeats (LRRs) and an LRR C-terminal (LRRCT) domain. LRRs have a broad spectrum of functions including cell adhesion and signaling, extracellular-matrix assembly, platelet aggregation, neuronal development, RNA processing, and immune response (3-5).

Herein, we aimed to present two siblings that presented with hair, skin, and eye hypopigmentation in addition to nystagmus, decreased visual acuity, and frequent recurrent infections, and were diagnosed with OCA Type 7.

CASE PRESENTATION

CASE 1

A 6.5-year-old girl patient presented to our clinic with complaints of hypopigmentation, nystagmus, mouth sores, oral candidiasis, and infection when she was three months old. She was born at term weighing 3000 grams with cesarean section. Family history revealed a kinship between the parents. In addition, a cousin who lives in the Netherlands had similar complaints. The family tree of the patient is given in Figure 1. Her height and body weight were in the 10-25th percentile range. Physical examination revealed albinism, nystagmus (Figure 2), oral aphthae, and oral candidiasis.

Laboratory examination results were hemoglobin (Hb): 12.6 g/dL, hematocrit (Hct): 37.8%, leukocyte count (WBC): 10260/mm³, platelet count: 279000/mm³, absolute neutrophil count (ANC): 3370/mm³, absolute lymphocyte count (ALC): 5800/mm³, peripheral eosinophil count: 90/mm³, C3: 0.91 g/L, C4: 0.234 g/dl, and CH50: 76%. The biochemical tests, C-reactive protein (CRP), and erythrocyte sedimentation rate were normal. Additionally, the patient's serum iron, iron-binding capacity, ferritin, folic acid, and Vit B12 levels were normal. Measurements made at 6 months of age were IgG: 906 mg/dl, IgA: 50.6 mg/dl, IgM: 102 mg/dl, IgE: 42.6 IU/ml, anti-Hbs antibody: 109 mg/dl, anti-measles IgG antibody: positive, anti rubella IgG antibody: positive, anti mumps IgG antibody: negative. The results of the lymphocyte subgroup analysis of the patient were CD3+: 56.7%, CD4+: 38.2%, CD8+: 18.0%, CD19+: 35.9%, CD20+: 38.6%, HLA-DR: 19.4%, CD16 + /56 +: 15%, CD45RA+: 86%, CD45RO+: 26%, CD18+: 100%, and CD15+: 99.9%. The lymphocyte stimulation test and dihydrorhodamine 123 test were normal. Skin prick testing, the Phadiatop assay, and fx5-specific IgE measurement to test allergic

sensitization were all negative. There was no pathological finding in the metabolic disease screening tests. Magnetic resonance imaging of the brain/pituitary gland revealed a 10x3x3 mm microadenoma in the pituitary gland. The patient was evaluated in a multidisciplinary fashion. Pediatric rheumatology and pediatric gastroenterology departments evaluated the case for recurrent oral aphthae, and no pathological finding was detected. The patient who had clinical manifestations of albinism and nystagmus was also consulted with the ophthalmology clinic. Visual acuity was 20/200 in the right eye and 20/200 in the left eye, and nystagmus was present on eye examination. Slit-lamp examination revealed bilateral iris transillumination defect, while fundus examination revealed bilateral chorioretinal atrophy and foveal hypoplasia, more prominent in the periphery (Figure 3A, B). Visual Evoked Potentials (VEP) examination was interpreted as "p 100 wave latencies were prolonged on the right but could not be obtained on the left. Patient incompatibility is prominent and clinical control is recommended three months later."

A homozygous mutation in the C10ORF11 gene (p.A23Rfs * 39) (p.Ala23Argfs * 39) was detected in the patient's genetic analysis performed for the diagnosis of OCA, and a diagnosis of OCA Type 7 was made. The cousin of the patient also had a homozygous mutation in the C10ORF11 gene.

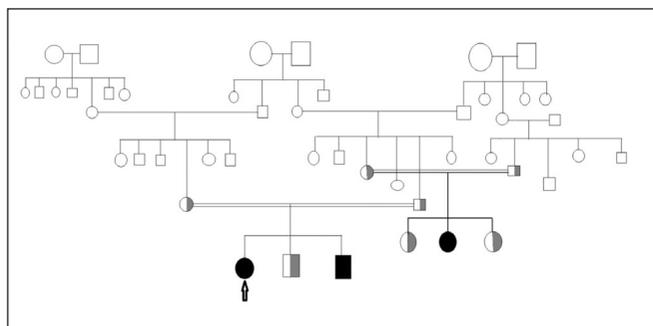


Figure 1. Pedigree of patients diagnosed with OCA type 7.



Figure 2. Clinical presentation of the patient. Patient presented with brown-white skin, brown-light yellow hair.

Results of the first-line immunological tests of the patient were within normal limits. However, prophylactic trimethoprim-sulfamethoxazole, fluconazole, and intravenous immunoglobulin (IVIG) were administered due to the ongoing complaints of recurrent oral aphthous lesions, oral candidiasis, and respiratory tract infections. After the treatment, the frequency of the infectious diseases decreased. Prophylaxis and IVIG treatment were discontinued because the patient's recurrent infections decreased in frequency after the age of five and a half years.

CASE 2

A 19-month-old boy patient was born by cesarean weighing 2720 grams at 37 gestational weeks as a borderline preterm baby. He was treated for ten days in the neonatal unit as nasal congestion, rapid breathing, and wheezing

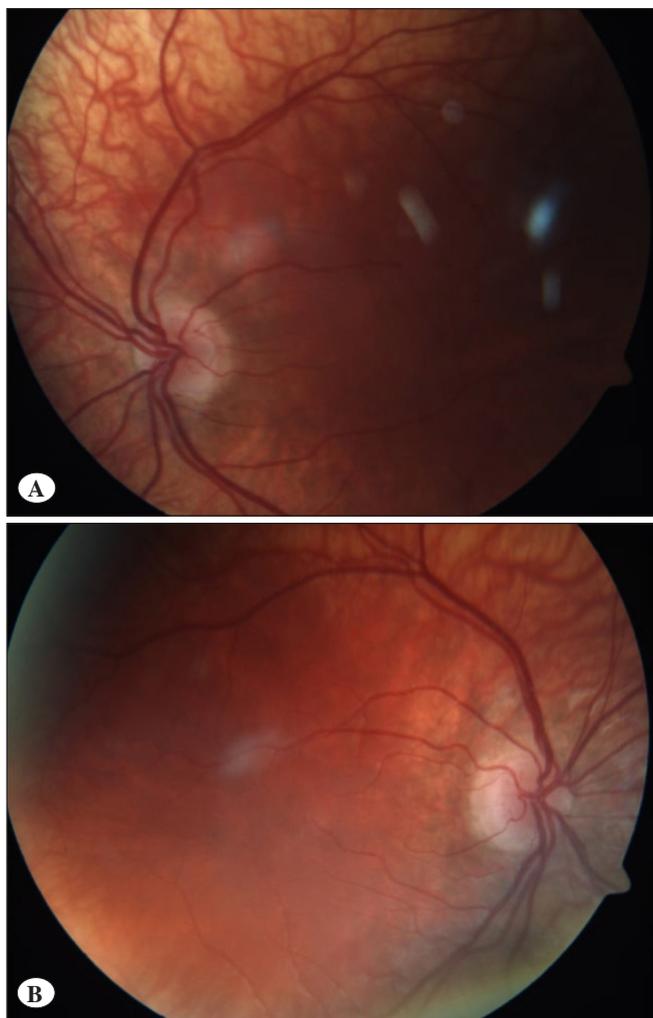


Figure 3. A) Patient's left fundus image, B) Patient's right fundus image (fundus examination revealed foveal hypoplasia and bilateral chorioretinal atrophy, more prominent in the periphery).

started on the first day after birth. When he was one month old, he applied to our clinic with a rash on her cheeks and arms. Later, the patient had a history of ten hospitalizations for recurrent respiratory and gastrointestinal infections in one year.

We detected the patient's height and body weight in the 3rd to 10th percentile range on physical examination. System examination revealed albinism, nystagmus, syndactyly between the second and third fingers of both feet, a 4x3 cm hyperpigmented lesion on the right lower abdominal quadrant (Figure 4), and erythematous, scaly, and crusted lesions on the cheeks and arms.

Results of laboratory tests were Hb: 11.3 g/dL, Hct: 34.1%, leukocyte count (WBC): 7990/mm³, platelet count: 265000/mm³, ANC: 2100/mm³, ALC: 4040/mm³, peripheral eosinophil count: 490/mm³, C3: 1.24 g/L, C4: 0.16 g/dl, and CH50: 68%. The biochemical tests, C-reactive protein (CRP), and erythrocyte sedimentation rate were normal. In the six-month period, the following relevant measurements were made: IgG 393 mg/dl, IgA: 25.8 mg/dl, IgM 28 mg/dl, IgE 9.33 IU/ml, anti Hbs antibody 87 mg/dl, anti measles IgG antibody negative, anti rubella IgG antibody positive, anti mumps IgG antibody negative.



Figure 4. Clinical presentation of Case 2 at the age of 19 months (Patient presented with brown-white skin, brown-light yellow hair, syndactyly between the 2nd and 3rd fingers of both feet, 4x3 cm hyperpigmented lesion in the right lower quadrant in the abdomen).

The results of the lymphocyte subgroup analysis of the patient were CD3+: 74.9%, CD4 +: 43.5%, CD8 +: 30.3%, CD19 +: 12.8%, CD20 +: 14.6%, HLA-DR: 18.8%, CD16/56 +: 10.3%, CD45RA +: 61.8%, CD45RO +: 30%, CD15 +: 99.7%, and CD18 +: 100%. The lymphocyte stimulation test and dihydrorhodamine 123 test were normal. Sweat test results were within normal limits. Sensitization was not detected in the skin prick and patch tests performed with food. Phadiatop, fx5, cow's milk, and egg white specific IgE tests yielded negative results. Due to recurrent diarrhea, we consulted the patient with the pediatric gastroenterology department. There was no pathological finding. However, she was diagnosed with atopic dermatitis due to her skin findings. There were iris transillumination defects, foveal hypoplasia, or chorioretinal atrophy in the ophthalmology examination. The VEP test could not be performed because the patient was not cooperative.

Results of the screening immunological tests of the patient were within normal limits. However, his history revealed that the patient has been hospitalized due to recurrent respiratory tract and diarrhea complaints. Therefore, prophylactic trimethoprim-sulfamethoxazole and IVIG treatment was initiated, and the frequency of the patient's infection decreased. A genetic test was performed to diagnose OCA type 7 in the patient whose sister had a diagnosis of OCA type 7, and a homozygous mutation was detected in the C10ORF11 gene (p.Ala23ARgfsTer39) (p.A23Rfs *39). Our patient was diagnosed with OCA Type 7.

No clinical findings supported oculocutaneous albinism in the mother, father, or the four and a half year-old brother in the family. We found heterozygous mutations in the C10ORF11 gene (p.Ala23ARgfsTer39) (p.A23Rfs * 39) in the mother, father, and brother with genetic screening.

DISCUSSION

Oculocutaneous albinism type 7 was first described in several families (8 individuals) from the Faroe Islands of Denmark (p.Arg194=) and a patient of Lithuanian descent (c.66dup C) (3). Later on, five patients were reported, including those from Iran, the Arabian Peninsula, Turkey, Morocco, and Europe. To date, seven different mutations have been identified in the C10ORF11 (LRMDA) gene (5). The disease is characterized by hypopigmentation of the eyes, skin, and hair. Hair color ranges from light

blonde to dark brown. The diagnosis of OCA is based on the characteristic symptoms related to the eye and clinical signs of hypopigmentation of the skin and hair.

On the other hand, molecular testing is necessary to demonstrate gene defects to determine the OCA subtype due to the clinical confusion caused by the OCA subtypes. Our cases had light skin color and brown-light blonde hair color. A homozygous mutation in the C10ORF11 gene was detected in the genetic analysis performed, together with the typical skin and eye findings. The most fundamental change in the OCA is seen in the optic system. Aberrant pathway of the optic nerves with an excessive crossing of the optic chiasm is a characteristic finding. This characteristic finding results in strabismus and reduced stereoscopic vision. Eye findings include congenital nystagmus, iris transillumination, translucency, hypopigmented retinal pigment epithelium, foveal hypoplasia, decreased visual acuity (visual acuity ranging from 6/9-18 to 3/60), photophobia (mild), macular hypoplasia, optic dysplasia, atypical choroidal vessels, and very rarely peripheral ocular fundus pigmentation. Besides, the cortical visual response's cross-asymmetry is detected in the VEP test (2-8). In the study by Gronskov et al. (3), although ocular symptoms were predominant in OCA type 7 patients, all patients had nystagmus and iris transillumination. The peripheral ocular fundus has been found to have pigmentation that is too light. In general, photophobia was not a big problem in patients with OCA type 7 in this study. Similarly, nystagmus, mild photophobia, bilateral iris transillumination defect, chorioretinal atrophy, and foveal hypoplasia were present in both of our cases.

The C10ORF11 (LRMDA) gene encodes a 198 amino acid protein containing three leucine-rich repeat proteins (LRRs) and an LRR C-terminal (LRRCT) domain. LRRs have a broad spectrum of functions, including immune functions (4). LRR proteins also regulate innate immune system functions and are found in the structure of most immune receptors. LRR proteins are essentially required for recognition of pathogen-associated molecular patterns (PAMPs) by toll-like receptors (TLRs) and nucleotide-binding and oligomerization domain (NOD)-like receptors (9,10). Moreover, the C10ORF11 protein is involved in the Wnt / beta-catenin pathway (3,11,12). The wnt / β -catenin signaling plays a critical role in cell differentiation, growth, proliferation, survival, and immune cell functions (13). Wnt / β -catenin modulates the activation of TLRs, and has critical functions such as stimulation of regulatory T

cell (Treg) functions and suppression of T helper 1 (Th1) and Th17 cell responses (14). Despite these studies in the literature, the immune system functions of the C10ORF11 protein have not been fully elucidated.

There were recurrent infections in the medical history of our patients. We did not detect any pathology in the tests for immunodeficiency screening. We also investigated the recurrent infection etiology in our patients and there were no pathological findings to suggest alternative diagnoses. The six and a half year-old female patient had recurrent oral aphthous lesions, oral candidiasis, and respiratory tract infections since birth. The other patient had a history of 10 hospitalizations for recurrent respiratory tract infections and diarrhea within a year. Especially in the first case, the persistence of recurrent respiratory tract infections, oral candidiasis, and oral aphthae after one year of age strengthened the immunodeficiency suspicion. Therefore, we started IVIG and prophylactic treatment for our patients. When the infection frequency of our patients decreased with these treatments, we continued the treatments. Prophylaxis and IVIG treatment were discontinued because the first case's recurrent infections decreased after the age of five and a half years. The literature also states that immune globulin therapy could be tried in the patients with history of recurrent infections and clinically suspected immunodeficiency, even if basic immunological tests are normal (15). With the available data, we could not definitively rule out immunodeficiency in our patients. There is limited data in the literature regarding OCA type 7, probably because the condition is extremely rare. Currently, the immune system functions of the C10ORF11 protein have not been fully elucidated. Besides, frequent or unexpected infections and immunodeficiency have not yet been reported in OCA type 7 cases in the literature. Therefore, detailed immunological tests, including functional studies, are needed. However, in the case report, we wanted to draw attention to the history of recurrent infections in OCA type 7 patients.

Differential diagnosis of OCA type 7 cases should be made among syndromes with similar clinical findings such as ocular albinism (OA), and the Hermansky-Pudlak, Chediak-Higashi, Griscelli, Waardenburg syndrome type II (WS2), Cross-McKusick-Breen, and Elejalde syndromes. Except for the WS2, WS2, Cross-McKusick-Breen, and Elejalde syndromes, they all show autosomal recessive inheritance and are distinguished based on clinical and biochemical criteria. Hypopigmentation is

also observed in the Angelman syndrome and Prader-Willi syndrome, characterized by a deletion in 15q11 (16). However, mental retardation is an essential clinical finding in Prader-Willi and Angelman syndromes. Unlike OCA, hypopigmentation in OA is limited to blue-brown iris in the eyes. Also, nystagmus, strabismus, foveal hypoplasia, the abnormal crossing of optic fibers, and decreased visual acuity are mild in OA (17). The primary defect in Chediak-Higashi syndrome, Griscelli syndrome, and Elejalde syndrome is melanosome transfer impairment, characterized by silvery gray hair color. Additionally, symptoms related to bleeding diathesis are observed in the Hermansky-Pudlak and Chediak-Higashi syndromes (17,18).

OCA patients should have an eye exam at regular intervals because eyeglasses or contact lenses can improve vision. Photochromatic lenses, dark glasses, or wide-brimmed hats can help reduce photophobia. Bifocal glasses can often correct decreased visual acuity. Contact lenses or surgical intervention in the eye muscles can correct nystagmus. Studies on the ability of levodopa/carbidopa (L-DOPA) or lutein and zeaxanthin to improve vision in individuals with albinism are ongoing (3,5). Depending on the pigmentation status the patient can be given particular recommendations for skincare. For this, the extent of skin pigmentation should be evaluated. Special clothes and sunscreens can reduce the risk of sunburn, skin damage, and skin cancer. Regular skin checks are recommended for early diagnosis of skin cancer (2,3,5). Children with OCA should use books and school materials written and labeled with contrasting bold letters and optical instruments in school. Life expectancy is not limited in patients with OCA, and medical problems are generally not increased than those in the general population. The development and intellectual levels of the patients are within normal limits. Patients with OCA have normal fertility potential (1,3,5).

In conclusion, OCA type 7 is a rare genetic disease that should be followed up with a multidisciplinary approach in cooperation with the ophthalmology, pediatrics, dermatology, and genetics departments. In addition, despite the frequent infection history in both of our patients, we did not find any pathology in the basal tests for immunodeficiency screening. However, we wanted to draw attention to the history of recurrent infection in OCA type 7 patients, which is extremely rare.

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