Oculocutaneous Albinism, A Family Matter

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Abstract
Oculocutaneous albinism (OCA) is a group of autosomal-recessive conditions characterized by mutations in melanin biosynthesis with resultant absence or reduction of melanin in the melanocytes. Herein, we present a rare case of two Caucasian sisters diagnosed with oculocutaneous albinism type 1 (OCA1). On physical exam, the sisters had nominal cutaneous evidence of OCA. This case highlights the difficulty of diagnosing oculocutaneous albinism in Caucasians. Additionally, we emphasize the uncommon underlying genetic mutations observed in individuals with oculocutaneous albinism.

Introduction
Oculocutaneous albinism (OCA) is a group of autosomal-recessive conditions characterized by mutations in melanin biosynthesis with resultant absence or reduction of melanin in the melanocytes. Melanin-poor, pigment-poor melanocytes phenotypically present as hypopigmentation of the hair, skin, and eyes.1,2

There are four genes responsible for the four principal types of OCA. OCA type 1A (OCA1A) and OCA type 1B (OCA1B) are caused by a mutation in the tyrosinase gene (TYR) on chromosome 11q14.3,3,4 OCA type 2 is caused by a mutation in the OCA2 gene.5,6 OCA type 3 is caused by a mutation in the tyrosinase-related protein 1 gene (TYRPI), and OCA type 4 is caused by a mutation in SLC45A2 (a.k.a. MATP).7,8 OCA1A is considered the most severe type of OCA due to a complete absence of melanin production. OCA1B, OCA2, OCA3 and OCA4 are considered less severe, as they often show small amounts of pigment accumulation over time.4 Overall, there is significant clinical overlap between the variants of OCA. Thus, molecular diagnosis is often necessary to establish the specific OCA subtype. The clinical characteristics found in individuals afflicted with OCA type 1 include hypopigmentation of the skin and hair and the distinctive ocular changes characteristic of all forms of albinism.9 Decreased melanin production does not alter the development of skin, but it does alter the color. The absence of melanin in the eye, on the other hand, leads to anomalous development and function.2 The ocular changes associated with OCA include severe nystagmus, prominent photophobia, reduced pigmentation of the retinal epithelium and reduced visual acuity.1 A pathognomonic finding of albinism is misrouting of the optic nerve at the optic chiasm, resulting in strabismus and reduced stereoscopic vision.1,4 Mutations in the TYR gene may entirely abolish tyrosinase activity, resulting in OCA1A, or decrease the activity of the tyrosinase enzyme, resulting in the development of OCA1B. Clinically, the difference between OCA1A and OCA1B is seen over time, as OCA1B individuals often accumulate minor quantities of melanin and begin to display small amounts of pigmentation.2

Ultimately, OCA is considered a clinical diagnosis. The diagnosis is made if the individual has hypopigmentation of the skin or hair in conjunction with the aforementioned characteristic ocular signs. Molecular genetic testing is often used in combination with the clinical diagnosis to establish the specific genetic mutation and thus the OCA subtype.2 Approximately one out of every 17,000 people has one of the four types of albinism.3,5 We present a rare case of sisters diagnosed with oculocutaneous albinism type 1, emphasizing the uncommon genetic mutations we observed in these two individuals.

Case Report
Two Caucasian sisters were referred to our dermatology clinic after receiving a diagnosis of oculocutaneous albinism type 1. Patient A was a 2-year-old Caucasian female, and Patient B was a 5-year-old Caucasian female. On physical exam, the sisters had nominal cutaneous evidence of OCA (Figures 1, 2).

Patients A and B were diagnosed with OCA after a retinal specialist recommended genetic testing to identify the cause of the sisters’ underlying optical impediments. The mother initially identified optical difficulties in her younger daughter, patient A, around 8 weeks of age. She noticed the infant displaying nystagmus and an inability to track. At seven months, patient A began crawling, and it quickly became evident the infant could not see more than a few feet in front of her. The mother became increasingly concerned when, at one year of age, her daughter had difficulty seeing beyond 20 feet (6 m). At that time, the child was evaluated by an ophthalmologist, who told the mother nothing was structurally wrong. The mother insisted on further workup. The mother’s primary clue to the underlying abnormality was her older daughter, patient B, who did not display these apparent optical difficulties. Patient A was referred to a neuro-ophtalmologist at the University of Michigan. An electroretinogram (ERG) and magnetic resonance imaging (MRI) were conducted for the initial ruling out of Leber congenital amaurosis (LCA). The MRI displayed no abnormalities. The ERG identified normal cones but decreased rods. Patient A was referred to a retinal specialist, who recommended genetic testing.

Both children underwent molecular analysis for underlying genetic anomalies. The genetic testing was performed using PCR amplification and DNA sequencing in two directions. Quantitative PCR analysis was performed using the ABI TaqMan copy number assay and CopyCaller software. qPCR primers for the OCA1 gene were used for amplification and detection, namely Hs03778472_m1 (intron 4), whereas RNAse P was used as the reference.

Patient A was found to possess a heterozygous mutation and a heterozygous deletion in the OCA1 gene, namely c.1217C>T, and deletion of exon 4. Additionally, patient A was found to possess the c.21delC frameshift mutation in the C10orf11 gene. Patient B was found to possess the same heterozygous mutation and deletion in the
OCA1 gene, but she did not possess the c.21delC frameshift mutation in the C10orf11 gene. Both girls were found to have clinical and molecular findings consistent with OCA1. Both mother and father underwent molecular genetic testing. The mother was found to possess the c.1217C>T mutation and the father the deletion of exon 4.

To date, both patients are doing well and being monitored with close follow-up.

Discussion

To date, 12 genetic mutations have been identified in the development of albinism.6 OCA type I is caused by a mutation in the tyrosinase gene (TYR) on chromosome 11q14.3.5 The C10orf11 gene encodes a protein containing three behaviors of C10orf11 remain an enigma. The TYR gene mutation causes a complete or partial loss of the catalytic activity of tyrosinase.8

The current case emphasizes a rare molecular presentation of OCA type 1, increasing awareness of the condition’s varied clinical manifestations. Current literature on albinism suggests 90% of OCA1A patients have two mutations. Among OCA1B patients, 37% have two mutations, and 63% have only one. In both forms, less than 1% of patients have an exonic or whole-gene deletion identified after molecular review.9 Both of our patients possessed a deletion of exon 4. Additionally, patient A had a distinctive mutation in the C10orf11 gene. A mutation in the gene C10orf11 on chromosome 10q22.2-q22.3 is associated with a new form of OCA, known as OCA7. However, the specific structural and functional behaviors of C10orf11 remain an enigma. The C10orf11 gene encodes a protein containing three leucine-rich repeats (LRRs) that have a variety of functions including cell adhesion, extracellular-matrix assembly, neuronal development and RNA processing.10 The C10orf11 mutation was observed in patient A but is not sufficient for the diagnosis of albinism. It is currently unknown what effect, if any, this mutation will have on patient A’s clinical symptoms. It is our hope that case reports like this will inspire further research to identify the relationships between genetic and phenotypic variations in the development of OCA. Identifying the significance of unique genetic mutations causing OCA will be vital to the development of personalized medicine for patients with albinism.

An essential component of medical management for these individuals involves genetic counseling. As in all types of autosomal-recessive inheritance, these sisters will pass on one non-working copy of the OCA1 gene to all of their offspring. At minimum, their children will be carriers of the condition. Additional patient education and future partner genetic counseling should be encouraged. The optimal time to determine genetic risk and clarification of carrier status is before pregnancy occurs.4 This case highlights the value of a dermatology consultation in young patients with clinical features of hypopigmentation and/or ocular findings. As in this case, the initial diagnosis of ocucutaneous albinism was delayed until confirmed by an ophthalmologist aware of the spectrum of its clinical features. Delays can result in years of unprotected solar exposure in individuals at greater risk for the harmful effects of UV radiation. Patients with OCA type 1, due to a pigment reduction in hair and skin, often develop solar keratosis, basal cell carcinoma and squamous cell carcinoma.4 Additionally, and arguably most commonly, these patients may develop numerous actinic keratoses, predisposing them to squamous cell carcinoma.12,14 Morbidity is influenced by phenotype, education and resource availability. Dermatologic consultation is essential, as patients (and in juvenile cases, their parents) must be made aware of the importance of sun-protection in patients with OCA1. Extensive solar exposure without protection results in a cumulative increase in the risk of cutaneous neoplasms. Five to 10 minutes of sun exposure in individuals with OCA1 is considered substantial.4

It is also important to emphasize that while melanoma is rare in individuals with OCA, it does occur. In one case, a patient with OCA was found to have malignant amelanotic melanoma that developed from an intradermal nevus.15

Patients with OCA need to be screened regularly for changes to their skin. Ongoing surveillance is imperative, particularly in those whose visual impairments make it difficult to appropriately assess and monitor their own skin. Finally, patients and families should be assured that persons with OCA have normal intelligence, fertility and, with proper skin protection, natural lifespans.2

Conclusion

As with any genetic condition, a patient’s morbidity and mortality can be vastly improved with identification, education and support. In this case report, we showcase a rare genetic mutation observed in individuals with ocucutaneous albinism, aiming to provide additional information on an uncommon clinical entity to assist with early diagnosis and management.

References