Bilateral asymmetrical partial heterochromia of iris and fundus in Waardenburg syndrome type 2A with a novel *MITF* gene mutation

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A 3-year-old girl presented with bilateral asymmetrical partial heterochromia of iris and fundus. The parents also complained of bilateral hearing loss in the child. Suspecting an auditory-pigmentary syndrome, systemic and genetic evaluation was performed. The child had profound sensory-neural hearing loss. Targeted gene sequencing revealed a novel nonsense variation in exon 9 of the *MITF* gene (chr3:70008440A>T) that was pathogenic for Waardenburg syndrome (WS) type 2A. This case highlights the characteristics of the iris and fundus hypochromia, which may provide a clue toward the diagnosis of WS.

Key words: Hearing loss, heterochromia, Waardenburg syndrome

Waardenburg syndrome (WS) is an auditory-pigmentary syndrome caused by the absence of melanocytes throughout the body, including hair, iris, retinal pigment epithelium (RPE), skin, and stria vascularis of the cochlea.[1,2] There exist multiple variants of the syndrome with each having a characteristic mutation. Waardenburg syndrome type 2A (WS2A) is caused by a mutation in the *MITF* gene (microphthalmia-associated transcription factor), which is responsible for melanogenesis.[3] The loss of pigmentation can be complete or incomplete.[1] The authors describe a case of WS2A with a characteristic pattern of hypopigmentation of iris and fundus, caused by a novel variation in the *MITF* gene.

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Case Report

A 3-year-old girl of Indian origin presented with the difference in eye color and impaired hearing since birth. She was a single child born out of a nonconsanguineous marriage. There were no other systemic complaints.

On examination, the child had normal facial features and hair pigmentation [Fig. 1a] with small hypopigmented patches over the entire body [Fig. 1b]. The Cardiff visual acuity was 20/80 in both eyes. Slit-lamp examination revealed bilateral partial heterochromia (hypochromia) of iris. The right eye had normal brown iris with a sharply demarcated abnormal radial segment (hypochromia) superiorly [Fig. 2a]. The left eye had an abnormal iris (hypochromia) with a sharply demarcated normal radial brown segment superiorly [Fig. 2b]. Wide-field fundus imaging (Optos Tx 200, Optos Inc.) revealed pigmentary changes corresponding to those found on the iris. The right eye fundus had a depigmentation of the superior quadrant extending from the disk and macula to the periphery with prominent choroidal vessels [Fig. 2c]. The left eye fundus had diffuse depigmentation except for a sector superiorly with normal pigmentation [Fig. 2d]. The optical coherence tomography did not reveal foveal thinning in both eyes.

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The examination of the child was performed after obtaining informed consent from the parents.

The parents did not have similar features. On systemic evaluation, the child had profound sensory-neural hearing loss (SNHL) and absent distortion-product otoacoustic emissions in both ears, suggestive of nonfunctional cochlear outer hair cells. The development was normal for the age. Suspecting an auditory-pigmentary syndrome, targeted gene sequencing was performed which revealed a heterozygous nonsense variation in exon 9 of *MITF* gene (chr3:70008440A>T; Depth: 87×) that resulted in a stop codon and premature truncation of the protein at codon 344 (p.Lys344Ter). This *MITF* variation was pathogenic for WS2A.

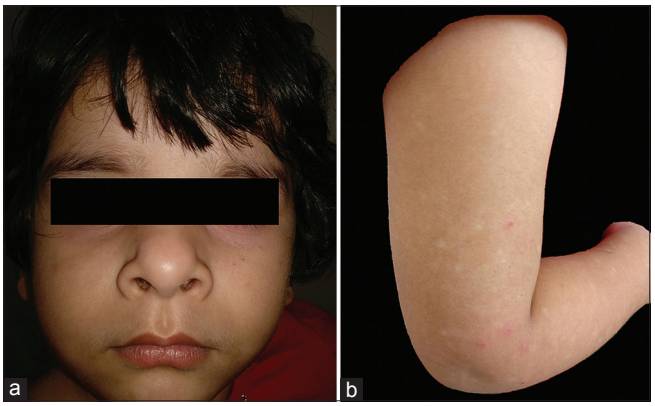

Figure 1: A case of Waardenburg syndrome type 2A. (a) Face photograph shows an absence of dysmorphism and absence of white forelock. (b) Right upper limb with multiple small areas of skin depigmentation

Cycloplegic refraction was performed and glasses were prescribed. The child is under active speech therapy and is planned for the cochlear implant.

Discussion

Oculocutaneous albinism (OCA) can be complete or incomplete.[1] Incomplete OCA can be associated with certain genetic syndromes such as WS.[1] While OCA has the abnormality in tyrosinase enzyme responsible for melanin formation,[2] auditory-pigmentary syndromes such as WS are caused by a physical absence of melanocytes throughout the body (hair, iris, RPE, skin, and stria vascularis of cochlea), which is usually patchy/incomplete.[3] WS variants 1, 3, and 4 are neurocristopathies (caused due to the failure of differentiation/migration/survival of neural crest cells), whereas WS2 is melanocyte-specific.[3]

WS2A is an autosomal dominant auditory-pigmentary syndrome with variable penetrance and expressivity and characterized by pigmentary abnormalities, congenital nonprogressive SNHL, and an absence of widely spaced inner canthus, that is, dystopia canthorum (commonly seen in WS1).[3] It is caused by a heterozygous mutation in the *MITF* gene (locus 3p14.1–p12.3).[3,4] The protein encoded by this gene regulates the melanocyte development and is responsible for transcription of melanogenesis enzyme genes.[4] Unlike the reported mutations for WS2A,[5] Lys344Ter variation is novel and is reported for the first time.

WS2A may have complete heterochromia (each iris has a different color) or more commonly partial heterochromia

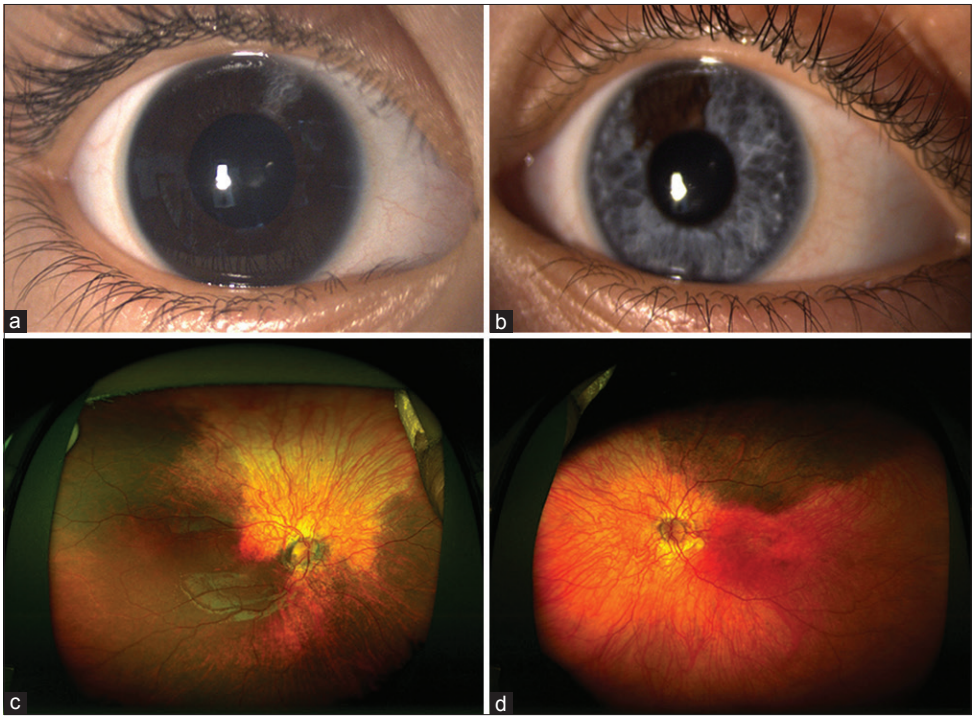

Figure 2: Ocular manifestations in a case of Waardenburg syndrome type 2A. (a) Slit-lamp photograph of right eye shows a normal brown iris with a sharply demarcated hypochromic segment superiorly. (b) Slit-lamp photograph of the left eye shows a hypochromic iris with a sharply demarcated normal brown segment superiorly. (c) Wide-field pseudocolor fundus image of right eye shows a sectoral depigmentation extending from the disk and macula to the superior periphery with prominent choroidal vessels. (d) Wide-field pseudocolor fundus image of the left eye shows diffuse depigmentation except for a sector superiorly with normal pigmentation

(differently colored area of the iris is usually a radial segment).[3] Partial heterochromia is found in up to 27.5% of patients with WS2.[3] Bilateral cases may be symmetrical or asymmetrical. The current patient had bilateral asymmetrical partial heterochromia. The right eye had a small superior area of iris hypochromia and a corresponding small area of RPE hypopigmentation. The left eye, on the other hand, showed large area of iris and RPE hypopigmentation. Thus, iris and RPE may be affected in a corresponding fashion.[3]

To conclude, this case highlights the characteristics of the iris and RPE hypochromia, which may provide a clue toward the diagnosis of WS. A novel mutation (Lys344Ter) in the *MITF* gene causing WS2 has also been identified.

Statement

The manuscript has been read and approved by all the authors, requirements for authorship have been met, and authors believe that the manuscript represents honest work.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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