Heterochromia caused by Waardenburg syndrome in a 2-month-old infant

Po-An Lin MD, Jia-Horung Hung MD, Yi-Hsun Huang MD PhD

■ Cite as: *CMAJ* 2024 March 11;196:E296. doi: 10.1503/cmaj.231616

A 2-month-old male infant was referred to our ophthalmology clinic because of his iris discoloration. We observed complete iris heterochromia, with dark brown in the right iris and blue in the left iris (Figure 1). A family history revealed hearing loss in both maternal and paternal grandparents. We evaluated the patient's auditory brainstem response and found left-sided hearing impairment. After consultation with a pediatric geneticist, subsequent whole-exome sequencing showed a heterozygous nonsense variant, c.1066C>T (p.Arg356Ter), in the microphthalmia-associated transcription factor (*MITF*) gene. We diagnosed Waardenburg syndrome, type 2A. We referred the infant for additional investigations to detect rare features of Waardenburg syndrome such as congenital heart abnormalities and Hirschsprung disease. Cardiac echocardiography, conducted when the infant was 5 months of age, showed a left-to-right atrial shunt, while abdominal ultrasonography was unremarkable.

Iris heterochromia is uncommon and can be congenital or acquired. The overall prevalence is estimated between 0.063% and 0.256%, with congenital heterochromia seen even less frequently.[1] Congenital heterochromia is often an isolated condition, without other systemic manifestations or anomalies. However, the differential diagnosis of congenital heterochromia includes Horner syndrome (ipsilateral ptosis, miosis, and facial anhidrosis), Sturge–Weber syndrome (port-wine birthmark), neurofibromatosis type 1 (café-au-lait spots, optic gliomas, and Lisch nodules), and Waardenburg syndrome (sensorineural hearing loss, pigmentary abnormalities, and musculoskeletal abnormalities).[2] Waardenburg syndrome can have varying expression of ocular manifestations in affected family members, where one may exhibit complete heterochromia while another may display partial heterochromia or no ocular manifestations.[3] Clinicians should consider syndromic associations for patients with congenital heterochromia and make referrals to both an ophthalmologist and genetic services. Genetic analysis — including whole-exome sequencing, targeted Waardenburg syndrome panels, or ocular disorder panels — is useful in the diagnosis of syndromes associated with congenital heterochromia.

Figure 1: Iris heterochromia in a 2-month-old infant, with dark brown in the right iris (normal-coloured eye) and blue in the left iris.

Competing interests: Yi-Hsun Huang reports funding from Taiwan's National Science and Technology Council (no. 111-2314-B-006-072-MY3). No other competing interests were declared.

This article has been peer reviewed.

The authors have obtained parental consent.

Affiliations: Departments of Ophthalmology (Lin, Hung, Huang) and Genomic Medicine (Hung), National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University; Institute of Clinical Medicine (Hung), College of Medicine, National Cheng Kung University.

Acknowledgement: The authors would like to express their gratitude to Dr. Meng-Che Tsai (Department of Pediatrics & Department of Genomic Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University) for consultation and interpretation of the genetic reports. Po-An Lin and Jia-Horung Hung are regarded as co-first authors for their equal contributions.

Correspondence to: Yi-Hsun Huang, jackhyh@gmail.com

References

1. Dabkowski M, Case J, Kloo I, et al. Estimating the prevalence of heterochromia iridum from high-resolution digital yearbook portraits. *J Optom* 2022;15:248-50.
2. Rennie IG. Don't it make my blue eyes brown: heterochromia and other abnormalities of the iris. *Eye (Lond)* 2012;26:29-50.
3. Li S, Qin M, Mao S, et al. A comprehensive genotype–phenotype evaluation of eight Chinese probands with Waardenburg syndrome. *BMC Med Genomics* 2022;15:230.

