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Blue-Eyed Asian: A Case Report of Waardenburg Syndrome Type 1

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Authors' contributions

This work was carried out in collaboration between both authors. Author ALDA designed and supervised the study. Author KZBA managed the literature searches, writing and editing of the paper. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To report a case of Waardeenburg Syndrome Type 1 presenting with bilateral blue iris in a young Asian.
Presentation of Case: A 7-year old Filipino girl was referred for ophthalmologic evaluation for bilateral blue eyes. She also presented with an eyebrow flare, broad nasal root, dystopia canthorum, heterochromic fundi and mild hearing loss. Her medical, developmental and family histories were unremarkable.
Discussion: Waardenburg Syndrome is a rare clinical disorder with oculocutaneous pigmentary anomalies, deafness and dystopia canthorum as major features. Diagnosed clinically using a Consortium criteria, this is one of the differential diagnoses when presented with a patient with bilateral blue eyes. There have been reports of this disorder in Asia but there are no known published articles or cases from the Philippines.
Conclusion: This is the first reported case of Waardenburg Syndrome in the country. This case

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presented with an atypical combination of bilateral blue eyes and heterochromic fundi in a young Asian girl.

Keywords: Waardenburg syndrome; blue iris; Pale blue eyes; heterochromic iris; heterochromic fundi, PAX gene; dystopia canthorum; hearing loss.

1. INTRODUCTION

Waardenburg Syndrome (WS), first published in 1951 by a Dutch ophthalmologist, is a rare genetic disorder with associated pigmentary anomalies of the hair, skin, eyes and minimal facial abnormalities, and congenital sensorineural deafness [1,2]. It approximately affects 1:40,000 population and comprises 3% of congenitally deaf children. It has no racial or ethnic predilection and with equal male to female ratio [3,4]. There have been reports of WS in Asia (e.g. Korea, India, Tokyo) but there are no known published articles or cases of the syndrome from the Philippines.

Table 1. Waardenburg syndrome consortium diagnostic criteria

Major criteria	Minor criteria
• Congenital sensorineural hearing loss • White forelock, hair hypopigmen-tation • Pigmentation abnormality of the iris o Complete heterochromia iridum o Partial/segmental heterochromia o Hypoplastic blue irides or brilliant blue eyes • Dystopia canthorum, Waardenburg index (W index) >1.95 • Affected first degree relative	• Skin hypopigmentation (congenital leukoma) • Synophrys/medial eyebrow flare • Broad/high nasal root, prominent columella • Hypoplastic alae nasi • Premature gray hair (age <30 years)

This syndrome is genetically and clinically heterogeneous, with four subtypes. WS Type1 (WS1) can be diagnosed using the WS Consortium Diagnostic Criteria (Table 1 above), with 2 major or 1 major plus 2 minor features fulfilled [1-6]. Type 2 lacks dystopia canthorum or the lateral displacement of the medial cathi. Type 3 is a severe form of WS Type1 with associated limb defects. Type 4 is characterized by Hirschsprung disease [2,7]. The characteristic features of WS1 are dystopia, broad and high nasal root, synophrys, partial or total heterochromic iris, white forelock and congenital deaf-mutism [7].

This is a case of a young Filipino girl, of pure Mangyan lineage, with an atypical WS1 presentation of bilateral blue iris and heterochromic fundi. This is the first known reported case of WS in the country.

2. PRESENTATION OF CASE

A 7-year old Filipino girl was referred for ophthalmologic evaluation because of bilateral blue eyes. Her prenatal, birth and developmental histories are unremarkable, with no history of medical illness or ototoxic drug intake. She is the second of three children of a non-consanguineous marriage. Family history is unremarkable. On physical examination, she has slim built with no facial, abdominal or limb anomalies. She presents with bilateral pale blue eyes, mild eyebrow flare and a broad nasal root (Figs. 1 and 2), with no skin and hair pigment anomalies seen anywhere in her body.

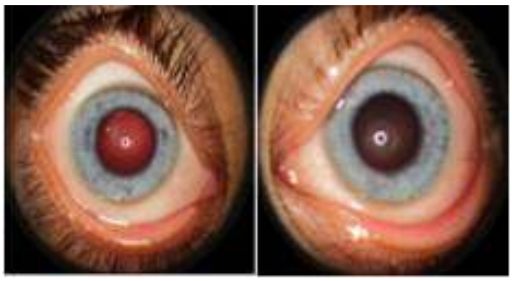


Fig. 1. Photograph showing the facial features of bilateral pale blue eyes, mild eyebrow flare, broad nasal root

Measurements for inner intercanthal, outer intercanthal and interpupillary distance were 31 mm, 78 mm and 52 mm respectively, with a computed W index of 2.0 for dystopia canthorum. Ophthalmologic examination revealed best corrected visual acuity of 20/25 OD and 20/30 OS, with 3 mm equally brisk reactive pupils, no nystagmus and relative afferent pupillary defects (RAPD). Cycloplegic refraction for OD is +1.00 D sph with -1.00 D cyl x180 and OS is +1.00 D sph.

Extraocular muscles were full OU. Slit lamp findings OU showed formed chambers, clear cornea and lens, bilateral pale blue iris with no transillumination defects. Intraocular pressure OU was 10 mmHg. Fundus examination demonstrated a heterochromic fundi with the right being hypopigmented and the left showing normal fundus color (Fig. 3).

A. Right eye **B. Left eye**

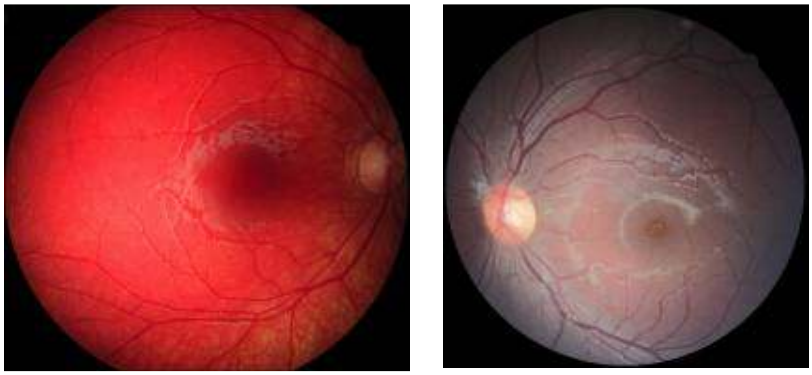
Fig. 2. Photos show both eyes with pale hypochromic color

Optical Coherence Tomograpy (OCT) was normal OU. Ear examination showed otoscopically normal findings, however, hearing test (play audiometry) revealed bilateral mild hearing loss. A pedigree was constructed for this index patient (Fig. 4), which showed no similar iris findings in the family. There are no known interracial marriages in the family. The evaluation of the family members was not performed due to inaccessibility and financial constraints. No genetic work-up was done. A clinical diagnosis of Waardenburg Syndrome Type1 was made based on its fulfillment of the Waardenburg Consortium Criteria for the said disease.

3. DISCUSSION

Waardenburg Syndrome is a rare disorder characterized with oculocutaneous anomalous pigmentations, deafness and dystopia canthorum, and abnormalities of neural crest derived tissues and its derivatives [2,3,5,7]. This syndrome is clinically heterogenous and expression of findings is extremely variable, thus the WS Consortium was created [2,3]. Using the criteria in this case, the index patient fulfilled 2 major (hypoplastic blue iris, dystopia canthorum) and 2 minor (mild synophrys, broad nasal root) features, establishing the diagnosis of WS1. The finding of bilateral mild hearing loss in the patient needs further testing (pure tone audiometry) to establish if it is sensorineural or of conductive origin, the latter being the feature of WS.

The bilateral blue iris is the most prominent feature in this patient. According to a 2011 report by Milunsky [3], the hypoplastic blue irides feature of WS patients is seen in only 15-18%, whereas the more common heterochromic irides is seen in up to 31% of patients. These iris discolorations are rarely seen in non-Waardenburg patients [8]. A histopathological study of the blue iris of WS patients showed reduced numbers of stromal melanocytes and smaller melanosomes compared to the fellow brown eye [9]. In Filipinos, of no known genetic disorders, and no interracial marriages, iris colors are gray or black. The differential diagnoses for bilateral blue eyes are ocular/oculocutaneous albinism, Fragile X syndrome, Angelman Syndrome, Prader-Willi Syndrome and Sturge Weber Syndrome. The absence of iris transillumination, nystagmus, cutaneous hypopigmentations, mental retardation or



A. Right eye **B. Left eye**

Fig. 3. Fundus of the right eye (A) shows hypopigmentation while the left eye (B) has a normal fundus color

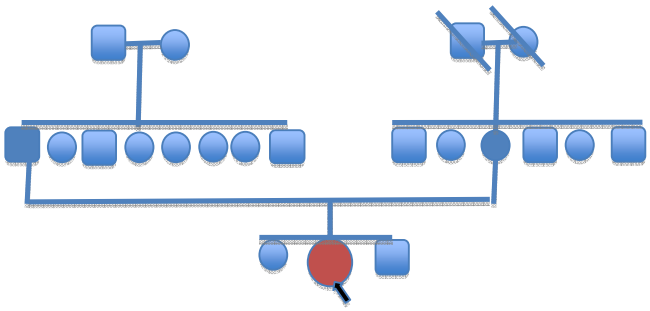


Fig. 4. Family genogram of the index patient

disability, unusual facies, and the patient's female sex have ruled out the diseases mentioned [10,11].

Among the clinical findings of WS, dystopia canthorum is the most penetrant feature of WS1, found in 99% of cases [2]. Dystopia canthorum is the lateral displacement of the medial canthi, and is confirmed when the W index exceeds 1.95 [3]. This can be computed with the following formula:

$$X = (2a - (0.2119c + 3.909)) /c$$
$$Y = (2a – (0.2479b + 3.909)) /b$$
$$W= X+Y+ a/b$$

*where

a = inner canthal distance (ICD), in mm
b = the interpupillary distance (IPD), in mm
c = the outer canthal distance (OCD), in mm

The patient's cephalomerics are ICD= 31 mm, IPD= 52 mm and OCD=78 mm. Comparing this to an age-based table of cephalometrics, using the Feingold and Bossert table [10], her IPD is within the 25-50 percentile; OCD is within 50-75 percentile, whereas her ICD is high at the 75 percentile. Also using these measurements, the computed W index of the patient is 2.0, confirming the presence of dystopia canthorum.

The medial eyebrow flare or synophrys is seen mildly in the index patient. This feature is usually seen in 63-73% of WS patients. The classic white forelock, early graying of hair and skin hypopigmentations or leukoma are absent in the patient. These are frequently seen in up to 48%, 38%, 36% of patients respectively [2,3]. The patient's heterochromic fundi, has been reported in some WS patients [7,8]. In a study by Ohno et al in Japan, two of their 11 patients presented with a combination of a normal and a hypopigmented fundi [12].

The most serious symptom in the clinical findings of patient with WS is hearing loss, seen in 47-58%. This is characterized as congenital, sensorineural type, typically non progressive, unilateral or bilateral. The hearing impairment may range from mild to profound, the latter may require deaf school attendance. This becomes an important prognostic factor because of possible impairment in the quality of life and cognitive abilities of the patient [1,3]. Silan et al. [13] screened 720 children with hearing deficits attending special schools in Turkey, and found 49 (6.8%) with WS. All were previously misdiagnosed to have a nonsyndromic deafness. In Japan, a screening of 240 children attending a school for hearing impairment showed 11 (4.6%) with WS Type 2 [12]. The hearing loss is due to the lack of melanocytes in the stria vascularis of the cochlea [5].

Inheritance of Waardenburg Syndrome is by autosomal dominance, with majority of the probands with affected parents. A minority does not have an affected parent, and may be presumed to be a *de novo* case [3]. An apparent negative family history cannot fully rule out WS until proper evaluation of the parents are done. The index patient has an unremarkable family history, however, no formal evaluation/examination of the index patient's parents and siblings was done, and is therefore recommended.

Multiple genes have been implicated in this syndrome, but particularly for WS Type1, the PAX3 gene is commonly affected, in up to 90% of those who meet the diagnostic criteria for WS [3]. Genetic work-up was not done in this patient due to financial constraints, and is recommended to confirm the clinical diagnosis of Waardenburg Syndrome Type1.

4. CONCLUSION

We have presented a case of a young Asian-Filipino girl with congenital bilateral blue iris, mild synophrys, dystopia canthorum, heterochromic

fundi and mild congenital bilateral hearing loss, which fulfills the criteria for the diagnosis of Waardenburg Syndrome Type1. This is an atypical presentation of the disorder with combination of bilateral blue eyes and heterochromic fundi, which has not yet been found in the review of literature. A genetic work-up of the patient and full evaluation of the parents are recommended to fully assess the extent and phenotypic-genetic correlations of this case.

CONSENT

All authors declare that written informed consent was obtained from the patient's legal guardian for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Tamayo M, Gelvez N, Rodriguez M, Florez S, Varon C, Medina D, et al. Screening Program for Waardenburg syndrome in Colombia: Clinical definition and phenoypic variability. Am J Med Genet Part A. 2008;146A:1026-1031.
2. Read AP, Newton VE. Waardenburg synrome. J Med Genet. 1997;34:656-665.
3. Gene Reviews. Milunsky JM. Waardenburg syndrome type 1. July 20, 2001 (Updated December 29, 2011). Available:http://www.ncbi.nlm.nih.gov/books/NBK1531/ (Accessed 10 November 2012).
4. Mehta M, Kavadu P, Chougule S. Waardenburg syndrome. Indian Journal of Otolaryngology and Head and Neck Surgery. 2004;56(4):300-302.
5. Choi JH, Moon S, Lee KH, Lew HM, Chang YH. Three cases of Waardenburg syndrome type 2 in a Korean family. Korean J Ophthalmol. 2004;18:185-189.
6. Wang J, Li S, Xiao X, Wang P, Guo X, Zhang Q. PAX3 mutations and clinical characteristics in Chinese patients with Waardenburg syndrome type 1. Molecular Vision. 2010;16:1146-1153.
7. Bist J, Adhikari P, Sharma AK. Waardenburg syndrome. Clin Exp Optom. 2011;94(2):240–242.
8. Eidenbock AM, Moser E, Frisch H, Read A. Waardenburg syndrome type 2 in a Turkish family: Implications for the importance of patterns of fundus pigmentation. Br J Ophthalmol. 2001;85: 1384-1393.
9. Rennie IG. Don't it make my blue eyes brown: Heterochromia and other abnormalities of the iris. Eye. 2012;26:29-50.
10. Jones KL. Smith's recognizable patterns of human malformation. Elsevier. 2006;407-412.
11. Gene Reviews. Lewis RA. Ocular Albinism, X-linked. March 12, 2004 (Updated April 5, 2011). Available:http://www.ncbi.nlm.nih.gov/books/NBK1343/ (Accessed 10 November 2012.
12. Ohno N, Kiyosawa M, Wang WF, Takase H, Mochizuki M. Clinical Findings in Japanese patients with Waardenburg syndrome type 2. Jpn J Ophthalmol. 2003;47:77-84.
13. Silan F, Zafer C, Onder I. Waardenburg syndrome in the Turkish deaf population. Genet Couns. 2006;17(1):41-8.

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