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Wardenburg syndrome type 2 in a woman with no genomic mutation commonly associated with the syndrome

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Abstract

Waardenburg Syndrome (WS) is a condition characterized by pigmentary changes of the hair or skin, hearing loss, heterochromia iridis, and dystopia canthorum. There are four main types of WS, which can be commonly caused by mutations in the *PAX3, MITF, EDNRB, EDN3, SNAI2*, or *SOX10* genes. Herein, we present a patient with Waardenburg Syndrome type 2 with no findings of mutations in the commonly associated genes.

Keywords: Waardenburg syndrome, dystopia canthorum, heterochromia iridis, nevus depigmentosus, hearing loss

Introduction

Waardenburg syndrome (WS) is a condition characterized by pigmentary changes, hearing loss, heterochromia iridis, and dystopia canthorum [1]. The incidence of WS is approximately 1/42,000; in any given patient, it can be inherited or occur de novo (Table 1), [2]. There are four main types of WS, which can be caused by mutations in the *PAX3*, *MITF*, *EDNRB*, *EDN3*, *SNAI2*, or *SOX10* genes (Table 1), [2].

Waardenburg syndrome has pigmentary effects related to dysregulated melanoblast migration from the neural crest to skin; this is controlled by genes implicated in WS listed above [3]. Other pigmentation defects include poliosis (circumscripta) and premature hair graying [4]. Additionally, neural crest cells differentiate into enteric neurons, resulting in gastrointestinal problems such as Hirschsprung disease that is also seen in WS [3]. Malformed extremities are another clinical manifestation of WS (**Table 1**).

Major and minor diagnostic criteria are specified for Waardenburg Syndrome type 1 (**Table 2**), [5]. However, the clinical definition of WS type 2 is less clearly delineated, resulting in a heterogeneous pool of individuals with pigmentary and hearing defects being considered WS type 2. We felt that our patient may best fall in this category [5].

Case Synopsis

An 18-year-old woman presented to clinic for treatment of acne and was found to have unusually colored irises; the left was mostly brown with blue sections and the right was mostly blue with brown sections (**Figure 1**). She also had a hypopigmented patch on the left mid-abdomen. Per her mother, she was born with bilateral blue irises, but by age three, her left iris started to turn brown. She was also noted to have hearing problems and began developing abdominal focal hypopigmentation at age six. The patient has no dystopia canthorum or white forelock. She has a family history of early onset alopecia (in her mother, starting at age 20) and blue irises and blonde

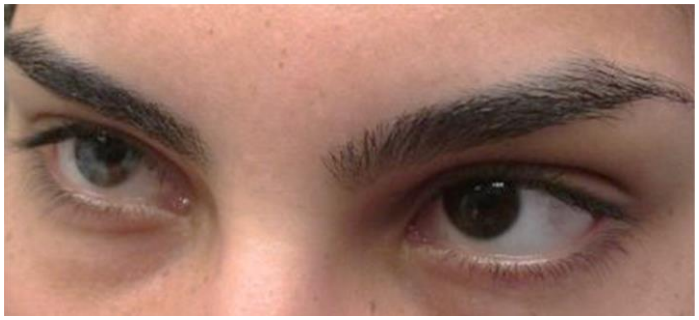

Figure 1. *Unusually colored. Left mostly brown with blue sections and the right was mostly blue with brown sections.*

hair in her maternal grandfather, despite her family's Argentine heritage. Given the clinical constellation, she was diagnosed with heterochromia irides and nevus depigmentosus concerning for Waardenburg syndrome type 2. Her hearing was evaluated by the otorhinolaryngology department and she was diagnosed with right-sided mild mixed hearing loss and left-sided sensorineural hearing loss. Given these findings, we pursued genetic testing for WS by panel array via Prevention Genetics for mutations in *EDN3, EDNRB, MITF, PAX3, SNAI2, or SOX10*. However,

Table 1. *Waardenburg Syndrome Types 1-4: Genetic and Clinical Findings.*

This table describes the four major types of Waardenburg Syndrome based on their genetics and clinical picture.

GENETICS	TYPE 1	TYPE 2 (a, b, c, d, e)	TYPE 3	TYPE 4
Gene(s)	PAX3	(a-c) MITF; (d) SNAI2; (e) SOX10	PAX3	(a) EDNRB; (b) EDN3; (c) SOX10
Locus	2q36.1	(a) 3p13; (b) 1p21-p13.3; (c) 8p23; (d) 8q11.21; (e) 22q13.1	2q36.1	(a) 13q22.3; (b) 20q13.32; (c) 22q13.1
Inheritance	AD	AD (a-c, e); AR (d)	AD; AR	AD (a-c); AR (a-b)
CLINICAL FINDINGS				
Pigmentary Changes				
	Hair White eyelashes/eyebrows (poliosis) White forelock of hair (poliosis) Premature hair graying **Skin** Hypopigmented skin lesions Congenital partial albinism (leukoderma) **Eyes** Heterochromia irides, complete or partial Hypoplastic iris stoma Hypopigmented ocular fundus Bright blue irides	**Hair** White eyelashes/eyebrows (poliosis) White forelock of hair (poliosis) Premature hair graying **Eyes** Heterochromia irides, complete or partial Hypoplastic iris stoma Hypopigmented ocular fundus	**Hair** White eyelashes/eyebrows (poliosis) White forelock of hair (poliosis) Premature hair graying **Skin** Hypopigmented skin lesions Congenital partial albinism (leukoderma) **Eyes** Heterochromia irides, complete or partial Hypopigmented iris Bright blue eyes	**Hair** White eyelashes/eyebrows (poliosis) Premature hair graying **Skin** Hypopigmented skin lesions **Eyes** Heterochromia irides, complete or partial Bright blue eyes
Hearing Loss				
	Congenital sensorineural deafness Aplasia of posterior semicircular canal	Congenital sensorineural deafness	Sensorineural deafness (progressive)	Sensorineural deafness (progressive)
Craniofacial Abnormalities				
	Dystopia canthorum (95-99%) Blepharophimosis Hypertelorism Synorphrys Smooth philtrum, decreased philtrum length High nasal root, wide nasal bridge Decreased nasal bone length, hypoplastic alae nasi Cleft lip/palate Prognathism	No dystopia canthorum Synorphrys Wide nasal bridge, hypoplastic alae nasi	Dystopia canthorum Blepharophimosis Synorphrys Prominent nasal root, hypoplastic alae Prognathism	
Characteristic Other Findings				
			Contractures of upper limb joints Hypoplasia of upper extremity bones Syndactyly, clinodactyly, brachydactyly Hypoplasia of hand muscles Finger contractures	Hirschsprung disease

AD=Autosomal Dominant; AR= Autosomal Recessive; (letter)=(subtype of WS type when specific for subtype)
References [4, 7-9]

Table 2. *Diagnostic Criteria for Waardenburg Syndrome Type 1.*
Waardenburg Syndrome type 1 diagnostic criteria from the Waardenburg Consortium.

Diagnostic Criteria for Waardenburg Syndrome Type 1
Major Criteria
-Congenital sensorineural hearing loss -Pigmentary disturbances of iris (complete heterochromia irides, partial segmental heterochromia irides, or hypoplastic blue irides) -White forelock/hair hypopigmentation -Dystopia canthorum -Affected first-degree relative
Minor Criteria
-Congenital leukoderma; areas of hypopigmented skin -Synophrys -Broad/high nasal root, low-hanging columella -Hypoplasia of alae nasi -Premature graying of hair (age <30 years)
The diagnosis of WS1 is established in a proband with two major criteria or one major plus two minor criteria (per the Waardenburg Consortium) [5].

these studies returned negative for causal mutations or variants of undetermined significance. Copy number variation analysis did not reveal duplications or deletions in the known WS genes. Whole exome sequencing was performed but showed no missense, nonsense, or splice site mutations in the WS genes.

Case Discussion

Typically, WS type 2 results from mutations in *SOX10*, *MITF*, or *SNAI2* [6]. Heterozygous *MITF* and *SOX10* point mutations or deletions have each been implicated in approximately 15 percent of cases and *SNAI2* in fewer cases [6]. This leaves a large number of unexplained etiologies for WS type 2 [4, 5], which suggests either more genes may be involved or that mutations within the known genes were undetected through previous screening methods.

With our patient's family history of pigmentary changes plus her unique phenotype closely fitting a diagnosis of WS (type 2), we are intrigued by her negative genetic analysis so far. Besides a false negative result, another explanation may be a small insertion, deletion, or point mutation in an enhancer, promoter, or repressor region of a known WS-associated gene. Other considerations include the possibility of mosaicism with expression within the skin. However, this does not necessarily explain her other systemic findings. Lastly, there could be a novel gene with a mutation resulting in the phenotype of WS as indicated in this patient.

Conclusion

Waardenburg syndrome has a spectrum of clinical findings, a unique configuration of which may be seen in a given patient. This case presentation led to clinical suspicion for Waardenburg syndrome type 2. However, the lack of genetic findings leads the authors to question whether an uncharacteristic mutation may be causative or if the clinical scenario is happenstance. Further potential avenues to evaluate this patient would be parental genetic analyses or whole genome sequencing of the patient to explore regulatory regions of known WS genes.

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