

Original Investigation | CLINICAL SCIENCES

Waardenburg Syndrome: Iris and Choroidal Hypopigmentation Findings on Anterior and Posterior Segment Imaging

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IMPORTANCE Waardenburg syndrome typically manifests with congenital iris pigmentary abnormalities, but careful inspection can reveal additional posterior uveal pigmentary abnormalities.

OBJECTIVE To demonstrate iris and choroidal hypopigmentation in patients with Waardenburg syndrome.

DESIGN, SETTING, AND PARTICIPANTS Retrospective review of 7 patients referred for evaluation of presumed ocular melanocytosis.

MAIN OUTCOMES AND MEASURES To describe the clinical and imaging features of the anterior and posterior uvea.

RESULTS In all patients, the diagnosis of Waardenburg syndrome was established. The nonocular features included white forelock in 4 of 7 (57%), tubular nose in 5 of 6 (83%), and small nasal alae in 5 of 6 (83%) patients. In 2 patients, a hearing deficit was documented on audiology testing. Family history of Waardenburg syndrome was elicited in 5 of 7 (71%) patients. Ocular features (7 patients) included telecanthus in 5 (71%), synophrys in 2 (29%), iris hypopigmentation in 5 (71%), and choroidal hypopigmentation in 5 (71%) patients. No patient had muscle contractures or Hirschsprung disease. Visual acuity was 20/20 to 20/50 in all patients. Iris hypopigmentation in 8 eyes was sector in 6 (75%) and diffuse (complete) in 2 (25%). Choroidal hypopigmentation in 9 eyes (100%) showed a sector pattern in 6 (67%) and a diffuse pattern in 3 (33%). Anterior segment optical coherence tomography revealed the hypopigmented iris to be thinner and with shallower crypts than the normal iris. Posterior segment optical coherence tomography showed a normal retina in all patients, but the subfoveal choroid in the hypopigmented region was slightly thinner (mean, 197 μm) compared with the opposite normal choroid (243 μm). Fundus autofluorescence demonstrated mild hyperautofluorescence (scleral unmasking) in hypopigmented choroid and no lipofuscin abnormality.

CONCLUSIONS AND RELEVANCE Waardenburg syndrome manifests hypopigmentation of the iris and choroid with imaging features showing a slight reduction in the thickness of the affected tissue.

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In 1951, Waardenburg published a description of a new syndrome of developmental anomalies of the eyelids, eyebrows, nasal root, iris, and scalp hair associated with congenital deafness, now called Waardenburg syndrome (WS).¹ In a 59-page document published in the *American Journal of Human Genetics*, Waardenburg delineated important distinguishing ocular findings. He opened his report with a description of a 72-year-old deaf-mute proband patient with epiphora from telecanthus. Waardenburg recognized the striking midline white hair of his patient and the family members. His second patient, found 1 year later from the clinic of Professor Franceschetti in Geneva, Switzerland, was a 10-year-old deaf-mute girl with telecanthus, a white forelock, and cutaneous “partial albinism.”

Waardenburg¹ further delineated the 6 chief characteristics of WS, including (1) telecanthus (lateral displacement of the medial canthus), (2) a broad nasal root, (3) synophrys of the eyebrows, (4) a white forelock (termed *piebaldism*), (5) heterochromia irides, and (6) deaf-mutism. In the initial description, Waardenburg described the eye findings as “heterochromia iridum totalis sive partialis,” with total or partial pigmentary disturbance. There was minimal comment on choroidal findings, with a minor remark that the choroid “seemed to take part in the pigment defect in a minor degree.”^{1(p240)} Subsequent studies have documented variable expressivity of the clinical findings in WS.^{2,3}

Not many publications have addressed the ocular features of WS, mostly focusing on the abnormalities of the iris. Few reports have presented details of the fundus findings, often with small-angle photographic documentation showing the macular region and without representation of the entire fundus.⁴⁻⁷ We have observed broad areas of choroidal hypopigmentation with WS. Herein, we document the striking iris and choroidal findings in patients with WS using wide-angle montage fundus photography, fundus autofluorescence, and optical coherence tomography (OCT). These ocular pigmentary features should be recognizable to the ophthalmologist, providing a clue to the underlying diagnosis.⁶

Methods

We reviewed the medical records of patients with a clinical diagnosis of WS, examined at the Ocular Oncology Service, Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania. Criteria for diagnosis of WS were based on the Waardenburg Consortium,⁸ indicating that affected individuals demonstrate at least 2 major criteria or 1 major criterion plus 2 minor criteria (Table 1).

The demographic information included patient age, race, sex, and family history of WS. Each patient was specifically examined for simulating conditions of ocular melanocytosis, albinism, vitiligo, autoimmune disease, previous inflammation, uveal or cutaneous melanoma, or other pigmentary conditions. The nonocular data included the presence of cutaneous pigmentary defects, deafness (confirmed by audiology testing), a tubular nasal bridge, and small nasal alae. The ocular data included visual acuity; the presence of telecanthus, synophrys, iris hypopigmentation, and choroidal hypopigmentation; and retinal and retinal pigment epithelial find-

Table 1. Diagnostic Criteria for Waardenburg Syndrome Type 1^a

Rank	Criteria
Major	Congenital sensorineural hearing loss; white forelock, hair hypopigmentation; iris pigmentation abnormality: complete heterochromia iridum, segmental heterochromia, or complete hypoplastic blue irides (brilliant blue irides); dystopia canthorum, W index >1.95; affected first-degree relative
Minor	Skin hypopigmentation (congenital leukoderma); synophrys/medial eyebrow flare; broad high nasal root, prominent columella; hypoplastic nasal alae; premature gray hair (age <30 years)

Abbreviations: W index, the measurements necessary to calculate the W index (in millimeters) are as follows: inner canthal distance (a), interpupillary distance (b), and outer canthal distance (c).

$$X = [2a - (0.2119c + 3.909)]/c.$$

$$Y = [2a - (0.2479b + 3.909)]/b.$$

$$W = X + Y + a/b.$$

^a Criteria proposed by the Waardenburg Consortium.⁸ An affected individual must have 2 major criteria or 1 major criterion plus 2 minor criteria.

ings. The iris was specifically assessed for intrinsic color and hypopigmentation features, including pattern (diffuse or sector), number of clock-hours, quadrant, and symmetry with the opposite eye. The choroid was specifically assessed for hypopigmentation features, including pattern (diffuse or sector), percentage of the affected fundus, largest basal diameter (in millimeters), quadrant, and symmetry with the opposite eye.

Imaging was performed (when necessary and available) using anterior segment OCT (AS-OCT) (Visante OCT 3.0; Carl Zeiss Meditec), with an illumination laser source of 1310 nm; posterior segment OCT (Heidelberg Spectralis HRA+OCT; Heidelberg Engineering); and fundus autofluorescence (Topcon TRC-50DX Retinal Camera; Topcon America), with an excitation light bandwidth of 535 to 585 nm and a barrier filter bandwidth of 605 to 715 nm. Wide-angle montage fundus photography was carried out when available. We compared the appearance and thickness of the iris tissue in the hypopigmented vs normal iris, OCT of the retina and choroidal features and thickness in the hypopigmented vs normal foveal choroid, and autofluorescence features in the hypopigmented vs normal choroid. Institutional review board permission from Wills Eye Institute was obtained.

Results

All 7 patients had bilateral findings. Patients included 5 (71%) whites, 1 (15%) Hispanic, and 1 (15%) African American, with 3 (43%) males and 4 (57%) females. The mean age at presentation was 32 years (median, 43 years; range, 1-66 years) (Table 2). Visual acuity was 20/20 in 10 (71%) eyes and 20/25 to 20/50 in 4 (29%) eyes. All 7 patients were referred with the presumed diagnosis of ocular melanocytosis.

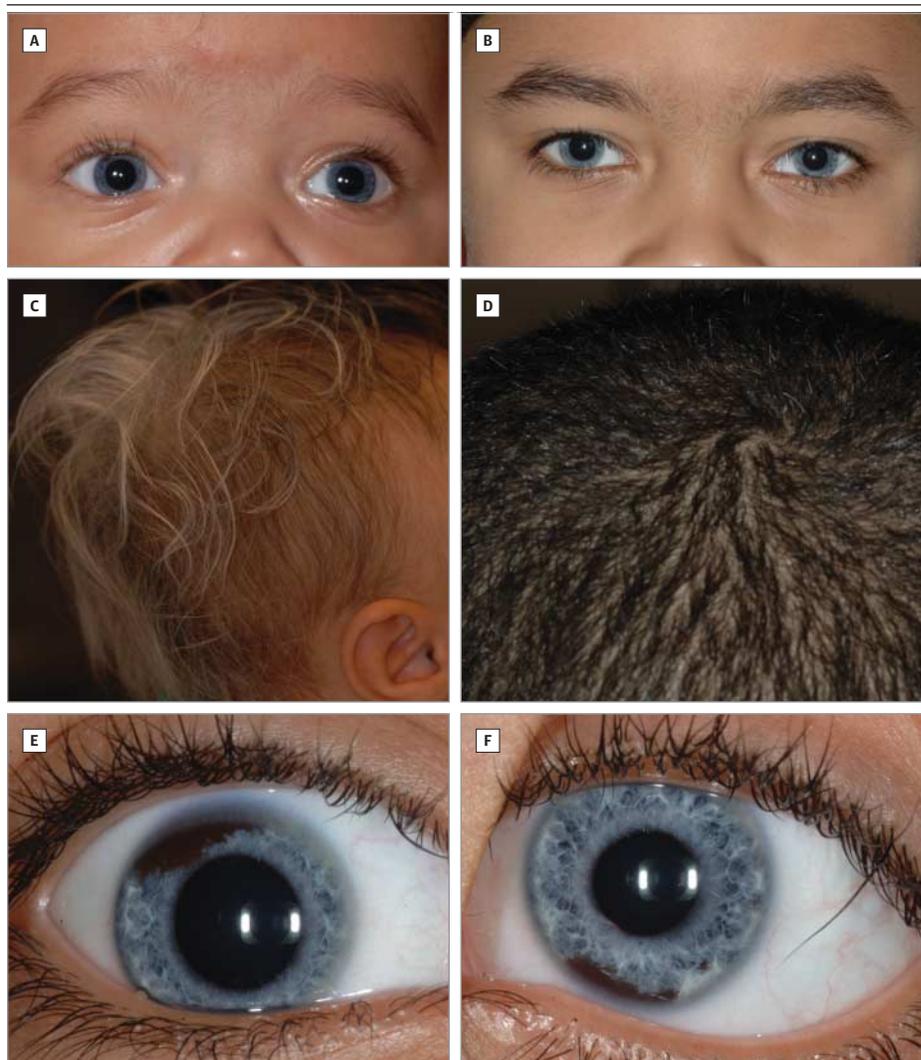
All patients met diagnostic criteria for WS (Table 1). No patient had muscle contractures (type 3 WS) or Hirschsprung disease (type 4 WS). The general manifestations of nonocular and ocular tissues are listed in Table 2. The ocular features include telecanthus in 5 (71%), synophrys in 2 (29%), iris hypopigmentation in 5 (71%), choroid hypopigmentation in 5 (71%), and focal retinal pigment epithelial loss in 4 (57%) patients (Figures 1, 2, and 3). The specific iris and choroidal

Table 2. General Manifestations of Waardenburg Syndrome in 7 Patients From 6 Families

Patient No./Race/Sex/Age, y	WS Criteria		Family History of WS	Nonocular Findings				Ocular Findings (General)				
	Major	Minor		White Forelock	Deafness	Tubular Nose	Small Nasal Alae	Telecanthus	Synophrys	Hypopigmentation		
										Iris	Choroidal	RPE Loss
1/H/M/66	3	4	Yes	Yes	NA	Yes	Yes	Yes	Yes	No	Yes	Yes
2/W/M/2	2	0	No	No	NA	Yes	Yes	Yes	No	Yes	No	Yes
3/W/F/43	3	2	Yes	Yes	NA	Yes	Yes	No	No	No	Yes	No
4/W/F/13	3	2	Yes	No	NA	Yes	Yes	Yes	No	Yes	Yes	No
5/W/F/47	4	3	Yes	Yes	Yes	NA	NA	Yes	No	Yes	Yes	Yes
6/AA/M/1	5	4	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
7/W/F/49	1	2	No	No	NA	Yes	Yes	No	No	Yes	Yes	No

Abbreviations: A, African American; F, female; H, Hispanic; M, male; NA, not available; RPE, retinal pigment epithelium; W, white; WS, Waardenburg syndrome.

Figure 1. Spectrum of Iris and Choroidal Hypopigmentation in a Lightly Pigmented African American Boy With Waardenburg Syndrome



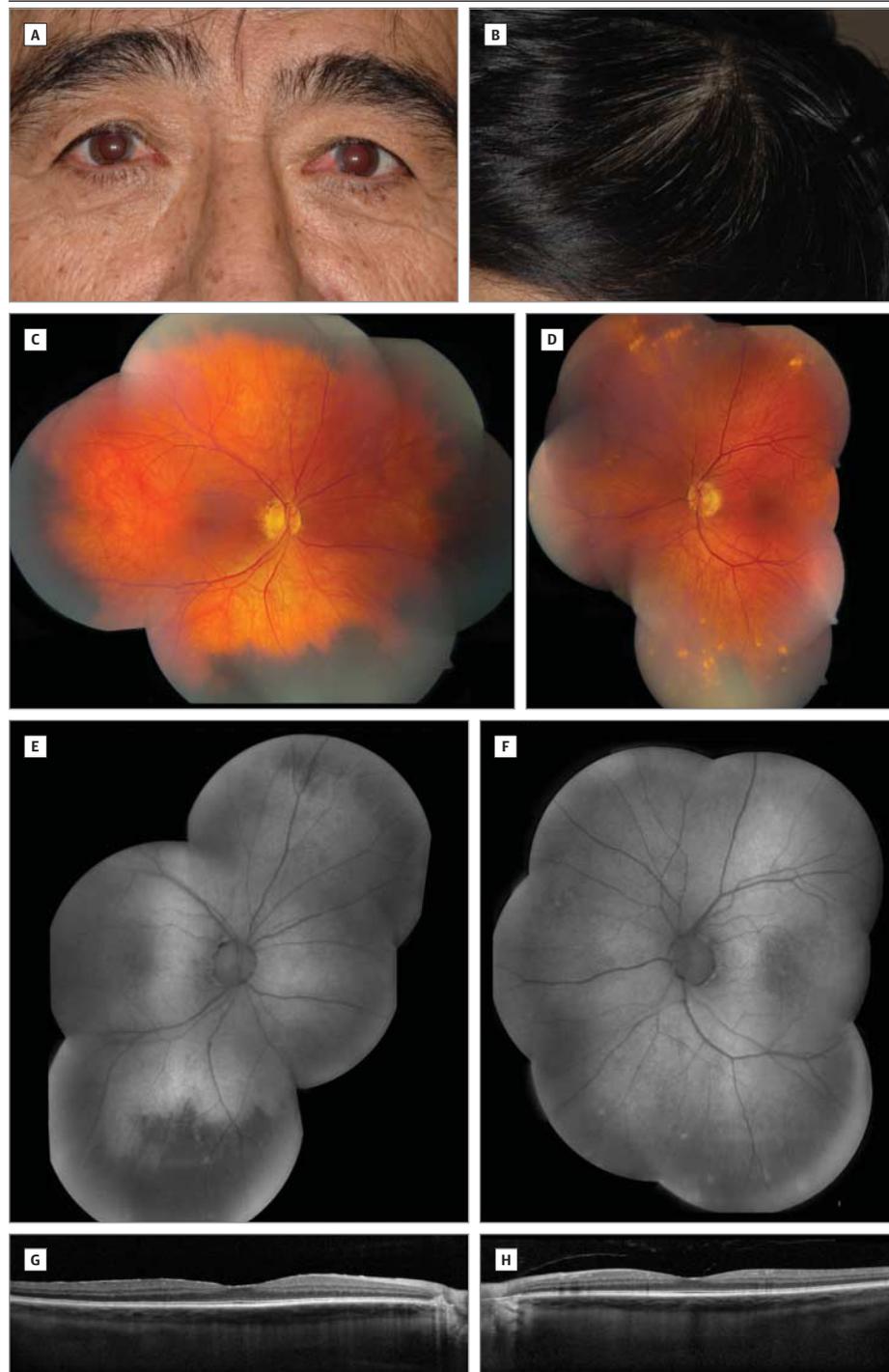
At age 1 year, blue irides, synophrys, and telecanthus (A) were noted and unchanged at 7 years (B). At age 1 year, a hypopigmented scalp forelock (C) evolved to scattered subtle white scalp hairs (D) at 7 years. At ages 1 and 7 years, the iris features were stable, with sector depigmentation involving nearly 11 clock-hours and with minimal residual brown superotemporally in the right eye (E) and inferonasally in the left eye (F), leaving brilliant blue irides of Waardenburg syndrome. Family members showed the same.

features are presented in Table 3. Of the 8 eyes with iris hypopigmentation, the pattern was sector in 6 (75%) and diffuse (complete) in 2 (25%) (Figure 1). The sector iris hypopigmentation involved 3 to 11 clock-hours (mean, 6.2 clock-

hours), with minimal symmetry of the pigmentary abnormality between the 2 irides.

Choroidal hypopigmentation, detected in 9 eyes, showed a sector pattern in 6 (67%) and a diffuse pattern in 3 (33%)

Figure 2. Choroidal Hypopigmentation in a Father and Daughter With Waardenburg Syndrome



A dark-haired 66-year-old Hispanic man with no iris defect, unrelated bilateral pterygium (A), telecanthus, mild synophrys, and congenital white forelock (B) treated with black hair dye. His daughter had the same white forelock but no eye examination. Wide-angle montage fundus photography documented a postequatorial hypopigmented choroid in the right (C) and left (D) eyes, with scattered focal retinal pigment epithelial atrophic spots. Fundus autofluorescence revealed slight hyperautofluorescence through the hypopigmented choroidal region in the right (E) and left (F) eyes, indicating unmasking of scleral autofluorescence. Enhanced depth imaging optical coherence tomography of the right (G) and left (H) eyes demonstrated normal retina in both eyes and slight thinning of choroidal tissue to approximately 175 to 180 μm in each eye.

(Figure 2 and Figure 3). The sector choroidal hypopigmentation was estimated using ophthalmoscopy at 20% to 80% (mean, 73%) of the fundus with a basal dimension of 10 to 22 mm (mean, 19 mm). The quadrants of choroidal hypopigmentation were postequatorial ($n = 2$), superotemporal ($n = 2$), nasal ($n = 2$), and the entire fundus ($n = 3$). All bilateral cases of choroidal hypopigmentation (8 eyes) had symmetry of the pig-

mentary abnormality. The iris hypopigmentation showed little correlation with choroidal hypopigmentation.

Using AS-OCT in 4 eyes, the hypopigmented iris was slightly thinner and with more shallow crypts than the normal iris (Table 4). Using posterior segment OCT, the subfoveal choroid was slightly (19%) thinner (mean, 197 μm) in the affected eye compared with the normal subfoveal choroid (243

µm) in the opposite eye. The retina was intact in all patients. Fundus autofluorescence demonstrated mild homogeneous hyperautofluorescence (scleral unmasking) in the hypopigmented choroid and no lipofuscin abnormality.

No patient showed features of albinism, vitiligo, autoimmune disease, previous inflammation, other pigmentary conditions, or ocular melanocytosis, including scleral, dermal, or palatal pigmentation. None of the patients had iris mammillations or equatorial drusen.

Discussion

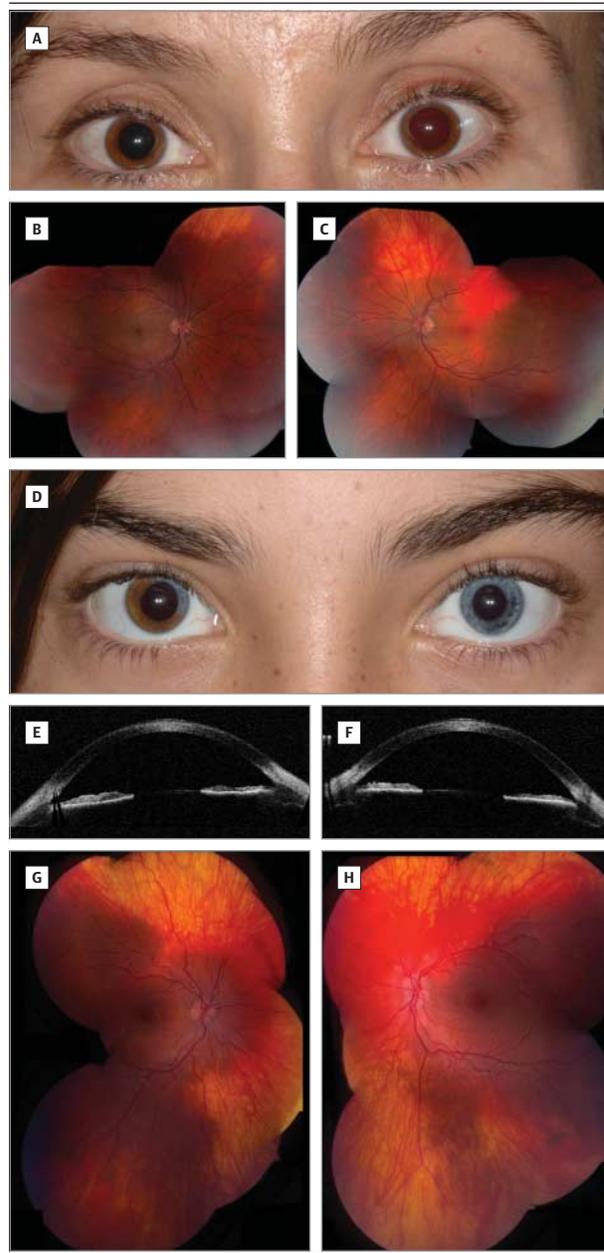
Waardenburg syndrome type 1 (WS1; OMIM 193500) is a highly penetrant autosomal dominant condition with major and minor features (Table 1). The phenotype of WS is variable, with 4 specific types, labeled WS1, WS2, WS3, and WS4.⁹ The features of WS1 include telecanthus; pigmentary abnormalities of the hair, skin, and eyes; and congenital deafness, as listed in Table 1. Those with WS2 are similar to patients with WS1 but lack telecanthus. Two much less common types include WS3 (Klein-Waardenburg syndrome), which also shows features of severe limb abnormalities and contractures, and WS4 (Waardenburg-Shah syndrome), with additional Hirschsprung disease. Identified genetic mutations in the *PAX3* gene can lead to WS1 and WS3.¹⁰⁻¹² Mutations in *MITF* and *SNAI2* lead to WS2. Type 4 WS is related to multiple mutations in *SOX10*, *EDN3*, or *EDNRB*.¹⁰⁻¹²

Clinical variability is common with WS, even within affected members of a single family.³ In an analysis of 26 patients diagnosed with WS1, features included telecanthus (82%), white forelock (24%), skin hypopigmentation (30%), iris heterochromia (32%), synophrys (78%), and hypoplastic nasal alae (92%).³ More severe deafness correlated with more extensive iris heterochromia.³

The ophthalmic pigmentary abnormalities in WS initially were described as iris heterochromia (complete or sector) and “minor choroidal findings.”¹ In 1966, Goldberg⁵ reviewed the ophthalmic findings in 14 patients from 7 families with WS and discovered a variety of sector and complete hypopigmentary features of the iris and the “fundus,” often parallel in the degree of pigmentation. For example, a blue iris was generally associated with a blond or “albino” fundus. Goldberg stated that the fundus pigmentary abnormalities constituted an integral part of WS. In 1978, Delleman and Hageman⁶ reviewed the ophthalmic findings in WS in 34 patients from 5 families and found 59% (20 of 34) with pigmentary disorders, including 15 with pigmentary iris abnormalities and 3 with hypoplastic blue irides bilaterally. Fundus examination revealed hypopigmentation in 67% (10 of 15).⁶ There was no further description of the extent, location, or pattern of alterations. Delleman and Hageman summarized their findings by stating that “10 of the 15 patients with pigmentary disorders of the iris also showed a shortage of pigment in the retina,”^{6(p345)} but we presume that it was actually the choroid.

There is some confusion in the literature about the terminology regarding the fundus and the external features. The term *piebaldism* has been used to denote the white forelock and loosely describes the pigmentary abnormalities of the iris. The word *piebaldism*, which implies *multicolored*, refers to the black

Figure 3. Features of Waardenburg Syndrome in a Mother and Daughter



A 43-year-old woman with no iris heterochromia (A) and sector choroidal hypopigmentation superiorly in the right (B) and left (C) eyes. The 13-year-old daughter had sector heterochromia (D) with anterior segment optical coherence tomography (horizontal orientation) documenting normal thickness of the normal brown iris (E) and a thin, flatter appearance of the affected, hypopigmented right (E) and left (F) irides. Funduscopically, there was symmetric choroidal hypopigmentation in the right (G) and left (H) eyes.

and white feathers of a magpie (*pie*), and the term *bald* indicates a white spot or patch.^{13,14} This term aptly describes the white forelock on a black-haired scalp. Furthermore, *piebaldism* is not descriptive of the iris or choroidal findings because these features do not involve black or white. A more appropriate term would simply be *hypopigmentation* since the normal brown or green iris is congenitally hypopigmented as blue.

Table 3. Specific Iris and Choroidal Findings of Waardenburg Syndrome in 7 Patients From 6 Families

Patient No.	Iris						Choroid					
	Eye	Iris Color	Iris Hypopigmentation				Choroid Hypopigmentation					
			Sector or Diffuse	No. of Clock-Hours	Quadrant	Symmetry	Sector or Diffuse	% Affected Choroid	Basal Dimension, mm	Quadrant	Symmetry	
1	OD	Brown	None	0	NA	NA	Sector	80	22	Posterior	Yes	
	OS	Brown	None	0	NA	NA	Sector	80	22	Posterior	Yes	
2	OD	Brown	None	0	NA	No	None	NA	NA	NA	NA	
	OS	Brown	Sector	3	Nasal	No	None	NA	NA	NA	NA	
3	OD	Brown	None	0	NA	NA	Sector	20	10	Superotemporal	Yes	
	OS	Brown	None	0	NA	NA	Sector	30	15	Superotemporal	Yes	
4	OD	Brown	Sector	5	Nasal	No	Sector	70	22	Nasal	Yes	
	OS	Blue	Diffuse	12	Diffuse	No	Sector	80	22	Nasal	Yes	
5	OD	Blue	Diffuse	12	Diffuse	No	Diffuse	100	24	Entire	Yes	
	OS	Brown	Sector	3	Superior	No	Diffuse	100	24	Entire	Yes	
6	OD	Brown	Sector	11	Inferior	No	None	NA	NA	NA	NA	
	OS	Brown	Sector	11	Superior	No	None	NA	NA	NA	NA	
7	OD	Brown	Sector	4	Temporal	No	Diffuse	100	24	Entire	No	
	OS	Brown	None	0	NA	No	None	NA	NA	NA	No	

Abbreviation: NA, not applicable.

Table 4. Ocular Imaging of the Iris and Choroid in Waardenburg Syndrome in 7 Patients From 6 Families

Patient No.	Anterior Segment Optical Coherence Tomography	Posterior Segment Optical Coherence Tomography			AF		
		Choroid Thickness in Normal Pigmented Fovea, μm	Choroid Thickness in Hypopigmented Fovea, μm	Retina	Hypopigmented Choroid	Lipofuscin (Orange Pigment)	Retinal Pigment Epithelial Atrophic Spots
1	...	175	NA	Normal	Hyper-AF ^a	None	Hyper-AF ^a
	...	180	NA	Normal	Hyper-AF ^a	None	Hyper-AF ^a
2

3	...	280	NA	Normal	Hyper-AF ^a	None	None
	...	NA	220	Normal	Hyper-AF ^a	None	None
4	Blue portion thinner stroma and with fewer crypts than brown portion	250	NA	Normal	Hyper-AF ^a	None	None
	Blue portion thin stroma	NA	190	Normal	Hyper-AF ^a	None	None
5

6	Blue portion thinner stroma and with fewer crypts than brown portion
	Blue portion thinner stroma and with fewer crypts than brown portion
7	...	NA	180	Normal	Hyper-AF ^a	None	None
	...	200	NA	Normal	Hyper-AF ^a	None	None

Abbreviations: AF, autofluorescence; ellipses, test not performed.

^a Slight.

The abnormalities of the iris in WS have been documented on electron microscopy to represent fewer melanocytes in the hypopigmented blue region compared with the normal brown region, and a substantial reduction in the melanosome size in the blue region is believed to be related to a defect in neural crest cell migration and melanin production.¹⁵ In our case series, 1 patient showed a bilateral “brilliant blue” iris, and 1 showed unilateral “blue” features. The remainder showed sectoral or no clinical defect in the iris. Imaging of the

iris with AS-OCT confirmed a slightly thinner iris with less obvious crypt formation in the depigmented “blue” region.

The choroidal pigmentary features were striking in this case series. Of the 7 patients with WS, 5 had choroidal hypopigmentation, which was often sectoral, involving large portions of the choroid with a symmetric distribution. Foveal OCT disclosed that the hypopigmented choroid was slightly (19%) thinner compared with the normal opposite subfoveal counterpart. Fundus autofluorescence displayed mild hyperauto-

fluorescence from slight unmasking of scleral autofluorescence, as seen with an amelanotic nevus.¹⁶ There was no visible lipofuscin abnormality on autofluorescence.

In addition to WS, several other conditions related to iris and choroidal pigmentary abnormalities can be included in the differential diagnosis. Some iris pigmentary abnormalities that could simulate the iris features of WS include iris freckles, nevus (circumscribed, sector, and diffuse), melanoma (circumscribed and diffuse), melanocytosis (sector and diffuse), Fuch heterochromic iridocyclitis, Horner syndrome, and topical medication (latanoprost). Some choroidal pigmentary abnormalities that could simulate the choroidal features in WS include choroid nevus, melanoma, melanocytosis (complete and sector), vitiligo, and Vogt-Koyanagi-Harada syndrome.¹⁷⁻²¹ Ocular melanocytosis most closely simulates the eye features of WS since both are congenital and can be unilateral or bilateral and diffuse, sectoral, or patchy. However, melanocytosis involves hyperpigmentation of uveal tissue, whereas WS involves hypopigmentation. In addition, hyperpigmentation of scleral, dermal, or palatal tissue often occurs in melanocytosis but is not found with WS. In melanocytosis, the darker portion of the iris can show dense mammillations with loss of crypts, the darker portion of the choroid eventually demonstrates drusen, and

there is a small risk for melanoma. With WS, there is the addition of family history, canthal location, and nonocular findings in the scalp, nasal bridge, and eyebrow. Furthermore, in WS, there is relative preservation of iris crypts, a lack of equatorial drusen, and no increased risk for melanoma. All 7 patients in this series were referred for evaluation of presumed ocular melanocytosis, and following our history and examination, the diagnosis of WS was established. All patients were recommended to have genetic evaluation, but each declined.

Limitations in our observations should be identified. We describe our findings in a small cohort of patients, but a larger cohort could provide more reliable results. In addition, our findings could be biased by referral due to our interest in pigmented lesions of the eye. The relative frequency of each finding would be better studied by examining a large cohort of patients with known WS. Furthermore, genetic testing was not obtained due to patient preference.

In conclusion, we have described and illustrated the broad spectrum of iris and choroidal hypopigmentation as part of WS. We have documented the features with wide-angle montage fundus photography, AS-OCT, posterior segment OCT, and autofluorescence. Despite the broad range of abnormalities in this condition, visual acuity generally remains intact.

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