Waardenburg syndrome (WS) is a rare genetic disorder with developmental anomalies of tissues derived from the neural crest and characterized by auditory and pigmentary findings. Failure of neural crest-derived melanocyte differentiation results in a spectrum of phenotypic presentations that are subdivided into 4 clinical types. We present a case of Waardenburg type 2 and briefly discuss the genetic basis of phenotypic expression of WS.

**CASE REPORT** An 18-year-old woman undergoing evaluation of intercostal neuralgia was incidentally noted to have one blue and one brown eye (figure). Both pupils reacted equally to light and accommodation. The patient’s mother reported that at birth both her eyes were blue but after 2 weeks the left eye changed to brown while the right eye remained blue. At birth she had a tuft of white hair on the frontal area. She had profound sensorineural hearing loss since birth and communicated via sign language. No other family member had this condition. Her mother’s eyes were brown and the color of her father’s eyes was unknown. The patient was subsequently lost to follow-up.

The differential diagnosis included oculocutaneous albinism, piebaldism, oculocerebral hypopigmentation syndrome, congenital Horner syndrome, neuroblastoma, and WS. Oculocutaneous albinism is characterized by generalized hypopigmentation of skin, hair, and eyes due to defective synthesis of melanin. Since the underlying defect is in pigment production rather than absence of melanocytes, these patients do not have sensorineural hearing loss. Piebaldism is characterized by a white forelock and multiple symmetric hypopigmented or depigmented macules but without developmental anomalies of the cochlea or interocular areas. The oculocerebral hypopigmentation syndrome is an autosomal recessive disorder characterized by the absence of pigmentation of skin and hair, microphthalmia, corneal clouding, and spastic paraplegia. Congenital Horner syndrome and neuroblastoma are rare causes of heterochromia irides, but no ptosis, miosis, or anhidrosis was observed in our patient. Moreover, neither of these conditions is associated with deaf-mutism or hair or skin hypopigmentation anomalies.

Given the presence of auditory and pigmentary findings since birth, a congenital syndrome involving melanocytic dysfunction was considered. The patient met 3 major and 1 minor Waardenburg Consortium diagnostic criteria (table) and a clinical diagnosis of WS type 2 was made.

**DISCUSSION** WS is a rare condition occurring due to maldevelopment of neural crest-derived tissues resulting in auditory, pigmentary, interocular, limb musculature, and enteric ganglia anomalies.

**Clinical features.** Four types of WS have been described, although phenotypic presentation may differ due to variable penetrance of the disease traits. WS1 and WS2 are characterized by one or more physical

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**Table** Waardenburg Consortium diagnostic criteria

<table>
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<tr>
<th>Major</th>
<th>Minor</th>
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<td>Congenital sensorineural hearing loss</td>
<td>Congenital leukoderma, synophrys, or medial eyebrow flare</td>
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<tr>
<td>Pigmentary disturbances of the iris</td>
<td>Broad high nasal root</td>
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<tr>
<td>Hair hypopigmentation</td>
<td>Hypoplasia of alae nasi</td>
</tr>
<tr>
<td>Affected first-degree relative</td>
<td>Prematurely graying hair</td>
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<tr>
<td>Dystopia canthorum</td>
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findings of the disease (table). The distinguishing feature between the 2 types is presence or absence of dystopia canthorum—an unusual facial feature in which the medial canthi of the eyes are spaced farther apart than normal, resulting in an appearance of widely spaced eyes. Ninety-eight percent of patients with WS1 have dystopia canthorum but patients with WS2 do not have this finding.3 WS3 (Waardenburg-Klein) phenotypes have hypoplastia of limb musculature and/or contractures of elbows and fingers,5 and WS4 (Waardenburg-Shah) phenotypes have Hirschsprung disease in addition to the other common features of WS.6

**Etiology.** Melanocyte dysfunction may be due to failure of neural crest differentiation, migration, or terminal differentiation and survival in target locations. Neural crest-derived melanocytes are essential to stria vascularis of the cochlea,7 which explains the sensorineural hearing loss observed in WS and preserved hearing in oculocutaneous albinism. Since retinal melanocytes are not derived from the neural crest but originate from the optic cup of the developing forebrain,7 they may serve as an important marker for differentiation of melanocyte-specific disorders as opposed to neurocristopathies. The limb muscles, frontal bone, and enteric ganglia are derived from the neural crest, which explains the phenotypic involvement of these structures in WS1, WS3, and WS4.

WS1 and WS3 are transmitted in an autosomal dominant fashion and nearly all cases have mutations in PAX-3 gene belonging to paired box family of transcription factors.7 Transcripts of PAX-3 are expressed in cells of the neural crest between day 8 and 17 of gestation.7 It is hypothesized that effective levels of PAX-3 protein determine the phenotype variation. Mild reduction in these proteins results in dystopia canthorum, 50% reduction results in melanocyte defects, and severe reduction results in limb anomalies.7 Hence WS1 and WS3 may actually represent phenotypic variations of the PAX-3 mutation depending upon the severity of suppression of the transcripts of PAX-3. WS2 is also transmitted in an autosomal dominant fashion, and about 15% of cases have a mutation in the microphthalmia gene MITF, while the molecular basis of the remainder of 85% is still unknown.8 MITF appears to be a master gene controlling melanocyte differentiation, and therefore WS2 is, at least in part, melanocyte specific.

WS4 is transmitted in an autosomal recessive manner and results from homozygous mutation of endothelin-3 (EDN3), its receptor (EDNRB), or SOX-10 (SRY-related HMG-box).8 Patients with heterozygous mutation of EDN3 or EDNRB have isolated Hirschsprung disease.8 The SOX10 gene directs the activity of other genes that signal neural crest to differentiate into melanocytes and enteric nerves.8 This explains the presence of Hirschsprung disease in patients with WS4.

**Prognosis.** Patients with WS have normal intelligence and they perform well on standardized speech tests following cochlear implantation and auditory rehabilitation. Early auditory rehabilitation is essential for normal cognitive development and is associated with excellent prognosis.9 Given the possibility of neural tube defects in patients with WS, folic acid supplementation is recommended in women with increased risk of having a child with WS.10

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