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Clinical Findings in Japanese Patients with Waardenburg Syndrome Type 2

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Purpose: To determine the visual characteristics of Japanese subjects with the Waardenburg syndrome type 2.

Methods: The visual functions of 11 albino patients who were identified from the screening of 240 children attending a school for children with a hearing deficit were studied. The ophthalmological examinations included eye position, visual acuity, biomicroscopy, ophthalmoscopy, visual field by confrontation or Goldmann's perimetry, stereoacuity by the Titmus test, and color vision by the Ishihara pseudoisochromatic plates.

Results: A combination of congenital sensory deafness and partial ocular albinism without lateral displacement of the lacrimal puncta was observed in 11 (4.6%) of the students with hearing deficit. All these children had sectorial heterochromia irides with local retinal hypopigmentation. Lid deformities were not present. The retinal vasculature was normal, and macular hypoplasty was not found. Other than 1 eye with hyperopic amblyopia, no serious visual disturbance was found in these patients.

Conclusions: The 11 students were classified as having Waardenburg syndrome type 2. None had a critical visual deficit, and all had partial heterochromia irides and retinal hypopigmentation. **Jpn J Ophthalmol 2003;47:77–84**

Key Words: Heterochromia irides, ocular albinism, retinal hypopigmentation, sensory deafness, Waardenburg syndrome.

Introduction

The syndrome of sensory deafness and albinism is referred to as the albinism-deafness syndrome or the Waardenburg syndrome.[1] Most cases of Waardenburg syndrome are accompanied by a lateral displacement of the lacrimal puncta, and are classified as Waardenburg syndrome type 1.[2,3] Patients with the Waardenburg syndrome but without a canthal deformity are categorized as having Waardenburg syndrome type 2.[3,4] Most of the reports on Waardenburg syndrome have been descriptions of single cases, or reports of the genetic mutation in these cases.[5–7] Based on these reports, the Waardenburg syndrome is not a homogenous disease,[2,8] but a syndrome correlated with the subnormal synthesis of melanin.

The visual characteristics of patients with this syndrome of albinism and deafness have not been well described. There has not been a consensus on the visual characteristics of patients with the Waardenburg syndrome. Only Liu and his coworkers have reported the ophthalmological findings in a series of 81 patients with this syndrome.[4] We shall present the visual characteristics of 11 Japanese patients with the Waardenburg syndrome type 2.

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Table 1. Clinical Findings in Waardensburg Syndrome Type 2 Subjects in This Study

Case No.	Age/Sex (y)	Visual Acuity (R/L*)	Extent of Iris Hypopigmentation (R/L*)	Area of Retinal Hypopigmentation (R/L*)	Remarks
1	5/M	0.7/0.7	Whole/whole	Whole/whole	
2	5/M	0.4/0.4	Whole/whole	Unknown	
3	9/F	1.0/1.0	Whole/whole	Whole/whole	
4	11/F	1.5/1.5	Whole/whole	Whole/whole	
5	14/M	(1.0)/(1.0)	Whole/whole	Whole/whole	Myopia OU
6	15/F	(1.0)/(0.7)	Whole/upper half	Whole/whole	Hyperopic amblyopia OS
7	16/F	1.5/1.5	Upper half/upper half	Normal/whole	
8	17/F	1.5/1.2	Upper half/upper half	Normal/lower half	
9	19/M	1.2/1.5	Upper half/upper half	Upper half/posterior pole	
10	18/F	0.9/1.2	Normal/whole	Upper half/whole	White frontal hair
11	19/F	1.5/1.2	Upper half/whole	Upper half/whole	

*Right eye/left eye.

Materials and Methods

Ophthalmological screening was performed on 240 children (ages 4–22) who had a hearing disability and attended a school in Chiba (kindergarten, primary, junior high, senior high, and junior college) for children with impaired hearing. In the screening session, 11 of the students were found to have some sign of ocular albinism, and all of them were confirmed to have sensory deafness from audiograms.

A complete ophthalmological examination was performed on these 11 students. The interocular index, that indicates the presence of *dystopia canthorum*, was obtained by the following formula to differentiate Waardenburg syndrome type 1 from type 2. Interocular index = intercanthal distance/interpupillary distance. Reported values of the interocular index were 0.57–0.70 in Waardenburg syndrome.[2,9] The uncorrected and corrected visual acuity and the eye position were determined. Stereoacuity was measured with the Titmus stereo test, and color vision was examined with the Ishihara pseudoisochromatic plates. The visual field was determined by a confrontation test, and Goldmann perimetry was performed when possible. Special attention was given to detecting a nasal visual field defect to determine whether a reduction of uncrossed fibers in the optic chiasma had occurred.[10]

Results

A summary of the ophthalmological findings in the 11 students with combined albinism and deafness are shown in Table 1. Eleven students (7 girls and 4 boys), 4.6% of the 240 students, had some sign of ocular albinism. All of them had congenital sensory deafness.

The shapes of their eyelids and ear auricles were normal, and a lateral displacement of the lacrimal puncta (*dystopia canthorum*) was not present in any of these subjects. All had hypopigmentation of the iris and retina. A simple combination of sensory deafness and ocular albinism was found in 10, and one female student (case 10) had a cluster of white hair in the frontal hair, the so-called "white locks" described in the textbook by Walsh and Hoyt.[11]

In all of the 11 students, the macula had a normal configuration, and all had good corrected vision except for one young girl who had hyperopic amblyopia. No exotropia or visual field defect was found in any of the students. Abnormalities were not found in the results of tests of eye position, stereoacuity, and color vision. Family history that may suggest family background was not present except in cases 7 and 9. Some typical cases are shown below.

Case Reports

Case 7. The parents of this 16-year-old girl were found to have congenital white patches on the iris in both eyes. Otherwise, the subject had no family history of deafness or eye disease. Although, she had had difficulty in hearing since birth, she did not have any visual complaints. Her natural hair color should have been black; her skin did not have any hypopigmentation. Her lacrimal puncta were not displaced. Her visual acuity was 1.0 (n.c.) in the right eye and 1.0 (n.c.) in the left eye. Heterochromia was present in the upper part of the iris in both eyes, and the interocular index was 0.55 (Figure 1). The right fundus was normal but the left fundus was diffusely red from hypopigmentation of the retinal pigment epithelium (Figure 2). Results of stereopsis, visual

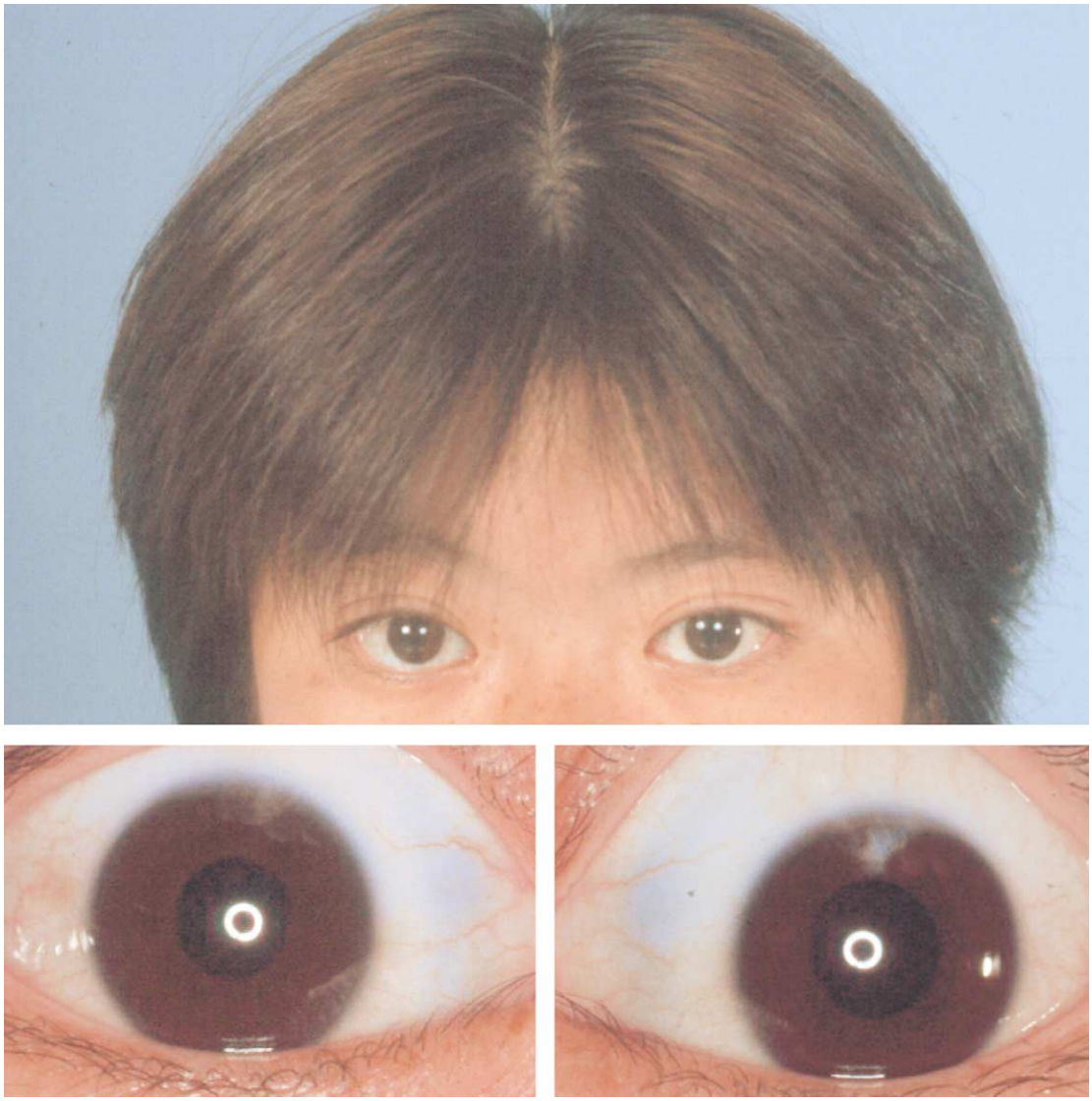

Figure 1. Hair and anterior view of the eyes of patient 7, a student of a school for children with hearing deficit, who showed symptoms of Waardenburg syndrome type 2. Normal hair color would be black. Wedge-shaped hypopigmentation of the iris (partial heterochromia irides) can be seen.

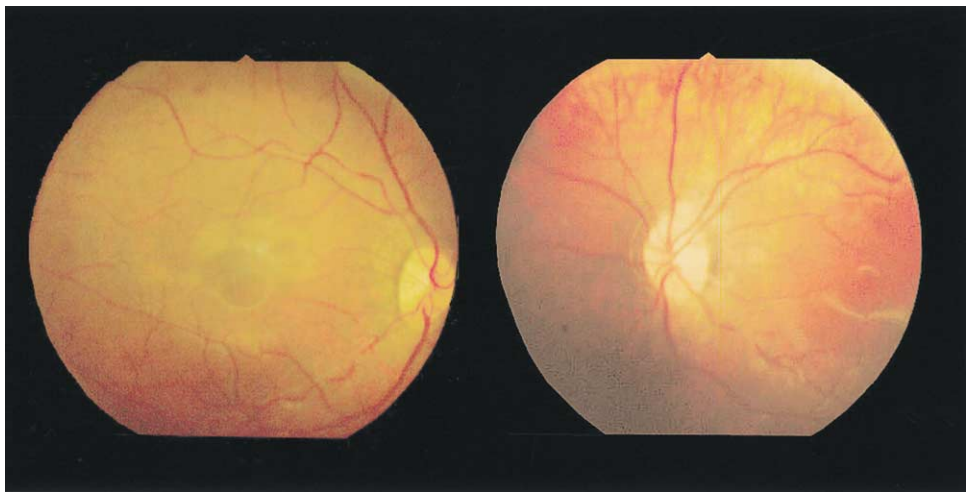

Figure 2. Fundus photographs of case 7. Hypopigmentation is present in the entire posterior pole of the left eye.

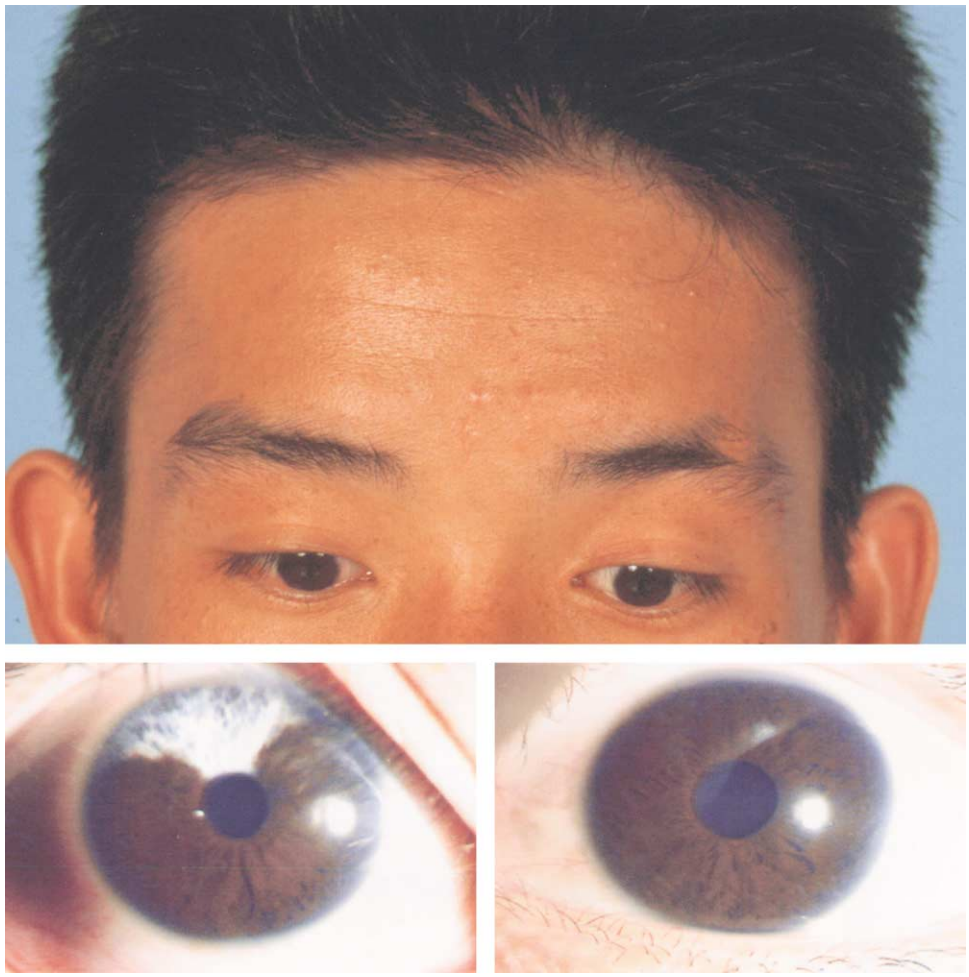

Figure 3. Hair and anterior segment of the eyes of patient 9. Hair color is normal, and iris in both eyes shows partial heterochromia.

fields, and color vision tests were normal. A diagnosis of Waardenburg syndrome type 2 was made.

Case 9. A 19-year-old young man had been deaf from birth. White marks on the iris were noticed by his parents in early childhood, and his mother also had congenital heterochromia irides. His father had acquired deafness following high fever as a boy. This student did not have hypopigmentation of the hair or skin.

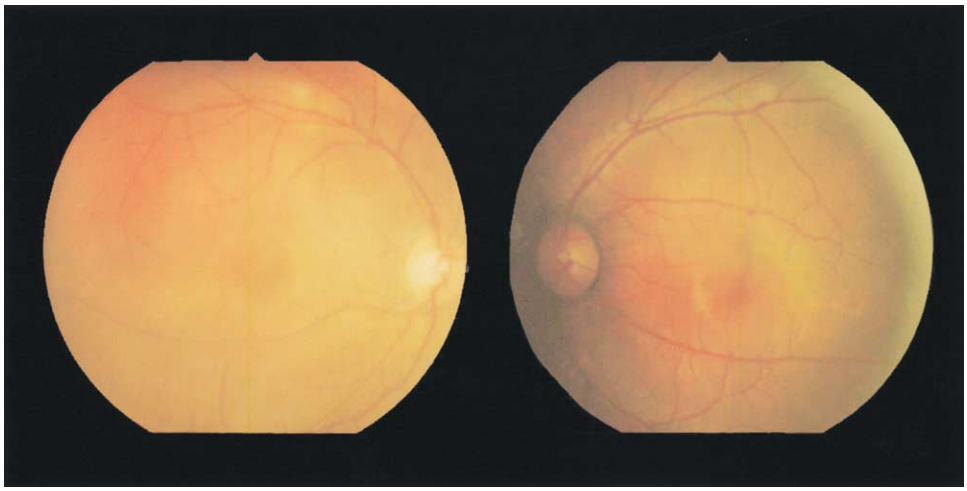

Figure 4. Fundus photographs of patient 9. Hypopigmentation is present in the entire posterior pole of the left eye.

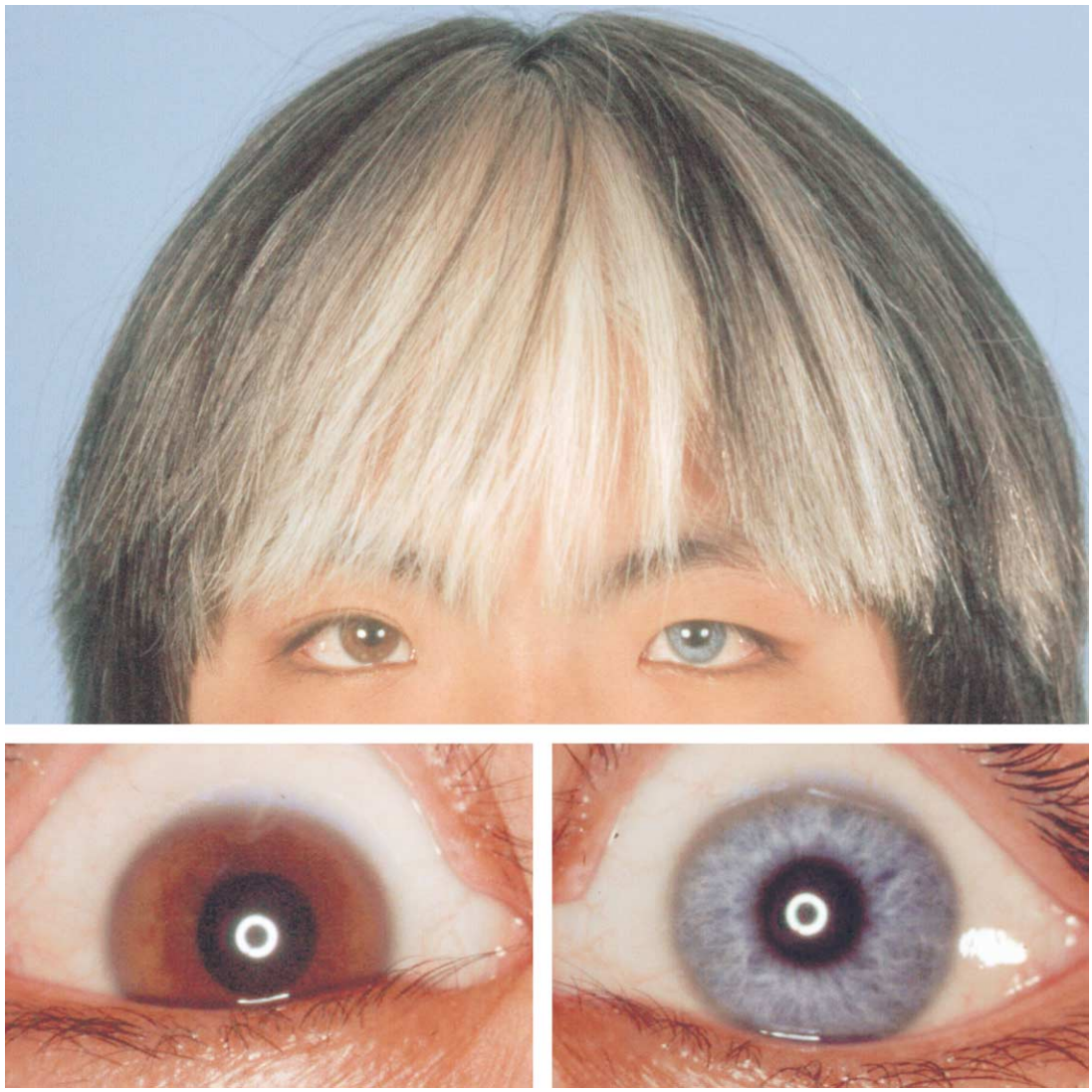

Figure 5. Hair and anterior segment of the eyes of patient 10. Clusters of white hair "white locks" can be seen in the frontal hair. The hypopigmented part of the right iris appears blue and the remaining portion is brown. Left iris was blue.

In the anterior segment, hypopigmentation was present on the upper half of the iris in both eyes. The lacrimal puncta were not displaced and the interocular index was 0.54 (Figure 3). Fundus examination revealed that hypopigmentation was present in the upper half of the right retina and the macular area of the left fundus (Figure 4). His visual acuity was 1.0 (n.c.) right and 1.0 (n.c.) left, and he had no visual difficulties. Visual fields, stereopsis, and color vision were normal. A diagnosis of Waardenburg syndrome type 2 was made.

Case 10. An 18-year-old young woman had a blue iris in the left eye congenitally but had no vision-related complaints. She had white locks only in the frontal hair. The lacrimal puncta were not displaced. The interocular index was 0.51 (Figure 5). Her corrected visual acuity was 0.9 in the right eye and 1.2 in the left eye. The upper half of the right iris showed partial heterochromia and the entire iris of the left eye was light blue in color. The right fundus showed hypopigmentation in the upper temporal periphery and the entire left retina was hypopigmented (Figure 6). Results of visual field and stereopsis tests were normal. No family members had deafness or albinism. A diagnosis of Waardenburg syndrome type 2 was made.

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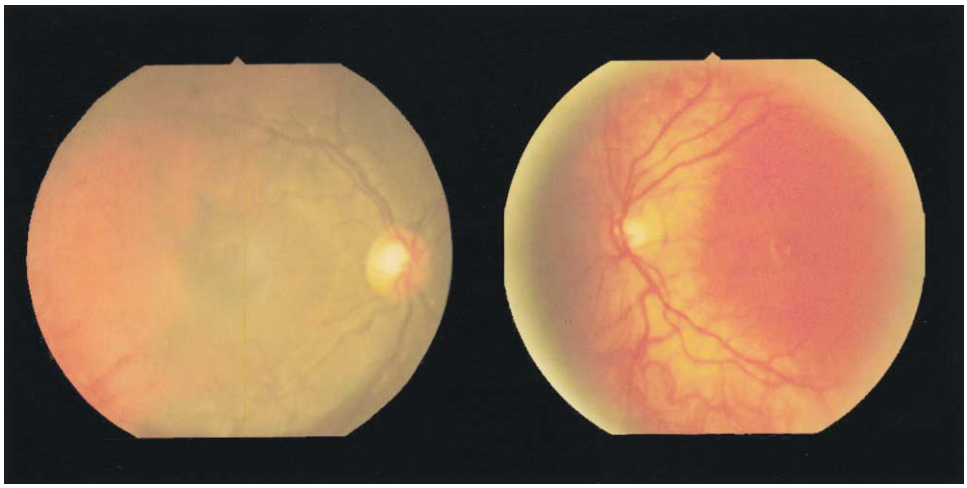

Figure 6. Fundus photographs of patient 10. The upper temporal part of the retina of the right eye and the entire left retina show hypopigmentation.

Discussion

The syndrome of albinism and deafness has a familial tendency and was first reported by Waardenburg in 1951.[1] Since then, there have been many reports on the syndrome. According to early reports, 98% of these cases had lacrimal puncta displacement and were classified as Waardenburg syndrome type 1.[2,3] None of our cases had lacrimal puncta displacement and, therefore, we searched the Japanese literature to determine whether the incidence of Waardenburg's syndrome type 1 was low in the Japanese population.[12–22] We have searched in a large population of patients with hearing disability. With our method of screening, we believe that even slight cases should not have been overlooked. We found that 4 of the 17 cases in the literature did not have a lacrimal puncta displacement, and these cases were classified as Waardenburg's syndrome type 2 (Table 2). Because of the small number of cases in our study, it is not clear whether type 2 is more common in Japanese cases of Waardenburg syndrome, or whether the lateral displacement of lacrimal puncta (*dystopia canthorum*) is not easily recognized in Japanese people.

Although all of our cases showed combined heterochromia irides and retinal local hypopigmentation, none of the students had low visual acuity or visual field defects. Partington et al screened for ocular albinism in a school for the deaf and identified 3 Waardenburg type 1 patients and 11 incomplete forms of the syndrome (4.1%) among the 343 deaf students.[9] The incidence was approximately the same as ours.

In our 11 cases, only two students (cases 7 and 9) had a family history of albinism or deafness, and an autosomal dominant transmission was suspected, similar to Bard's case.[8] An autosomal recessive transmission was considered to be inherited in the other sporadic cases. Several different genes have been proposed as candidate genes for the Waardenburg syndrome types 1 and 2, such as the SOX10,[5] the MITF promotor gene,[6] and the OC2 gene.[7] The most common type of ocular albinism is caused by an OA1 gene mutation and has an X-linked recessive inheritance pattern. Male patients who show the Nittleship-False type ocular albinism have definite ocular symptoms, such as nystagmus and decreased visual acuity due to macular hypoplasia. Female carriers of this gene have good visual functions although they have partially translucent iris, macular hypoplasia, and granular retinal appearance in the midperiphery.[23,24] The occurrences in our patients were in both sexes, but their ocular findings were quite similar to those of the female carriers of the Nittleship-False type of ocular albinism. Fried reported on a female carrier having sex-linked deafness with albinism.[25] There also is a report of a patient with ocular albinism and macular hypoplasia who had abnormal retinal vasculature and reduced visual acuity.[8]

An MITF gene mutation has been found in a patient with the Waardenburg syndrome type 2, and this gene is homologous to the mouse *mi* mutant allele at the molecular level.[26] This gene is believed to be present on the 3p12.3–p14.1 chromosome,[4,27] and thus, an autosomal transmission would be expected. The MITF transfer factor is also proposed as a gene related to this disease, and is suspected to be associated with the regulation of gene transcription spe-

Table 2. Clinical Findings in 17 Waardenburg Syndrome Cases Cited in Japanese Literature

Case No.	Age/Sex (y)	Visual Acuity (R/L)*	Iris Hypopigmentation (R/L)*	Retinal Hypopigmentation (R/L)*	*Dystopia Canthorum*	Remarks	Reference
1	11/M	(0.9)/0.7	Whole/whole	Normal/normal	Yes	Glaucoma OU, myopia OD	Fukuda et al[12]
2	7/F	(0.7)/(0.8)	Whole/whole	Whole/whole	Yes	Myopia OU, granddaughter of case 5	Tokuhara et al[13]
3	13/F	(1.0)/(0.9)	Normal/12′-3′	Normal/upper half	Yes	Hyperopia, sister of case 2	Tokuhara et al[13]
4	34/F	(1.2)/(1.0)	Normal/whole	Normal/whole	Yes	White frontal hair, myopia OU, mother of cases 2 and 3	Tokuhara et al[13]
5	54/F	(0.8)/(0.9)	Normal/normal	Normal/normal	Yes	Myopic astigmatism, grandmother of cases 2 and 3	Tokuhara et al[13]
6	12/M	1.2/1.2	Whole/whole	Lower half/whole	Yes	White hair	Ito et al[14]
7	1M/F	–/–	Whole/whole	Whole/whole	No		Nakamura et al[15]
8	9/–	(1.0)/(1.0)	Whole/normal	Whole/normal	Yes		Nakamura et al[15]
9	15/M	1.5/1.5	Whole/peripheral	Whole/normal	Yes		Morimoto et al[16]
10	2/M	–/–	Whole/normal	Whole/normal	Yes	Frontal white hair	Tsuchida et al[17]
11	2/F	0.7/0.7	Whole/3′-12′	Whole/whole	No	Daughter of case 12	Fujimori et al[18]
12	31/F	(1.5)/(1.5)	Normal/normal	Nasal/normal	Yes	Mother of case 11	Fujimori et al[18]
13	20/F	0.2/(0.9)	Whole/whole	Whole/whole	Yes	Retinal detachment OU	Kita et al[19]
14	12/M	–/–	Whole/whole	Unknown	Yes		Ito et al[20]
15	3/F	–/–	Whole/normal	Whole/normal	No	Sister of case 16	Noda et al[21]
16	6/F	–/–	Whole/whole	Whole/whole	No	Sister of case 15	Noda et al[21]
17	57/F	0.04/0.01	Normal/whole	Normal/whole	Yes	White frontal hair	Kimura et al[22]

*Right eye/left eye.

cific for pigment cells.[28] Genetic analysis has not been performed as yet in our cases, and these examinations will be needed. In the near future, a more complete classification for the syndrome of albinism and hearing loss will be provided by the further development of gene analysis.

Albinism is generally caused by a deficit of the enzyme that converts tyrosine to melanin. Therefore, it is not very surprising to find deafness and ocular albinism in the same patient because the hair cells in the inner ear and the retinal pigment epithelium have melanosomes. Patients with hypopigmentation of the retinal pigment epithelium without macular hypoplasia do not show reduced visual acuity.

Among patients with albinism and deafness, some have been reported with a family history. In some of these patients, iris hypopigmentation, malformation of the facial features, and genetic mutations were present. Nevertheless, the visual acuity and other visual functions were normal. All of our students with Waardenburg syndrome type 2 had normal visual acuity, visual field, stereopsis, and color vision. These findings suggest that there may be many patients hidden in the deaf population with defective pigment synthesis that causes deficits in the inner ear and in the pigmentation of the eye, but without any other symptoms of Waardenburg syndrome.

Conclusions

Eleven of the 240 students attending a school for children with hearing deficits were found to have partial ocular albinism associated with deafness. None had a lateral displacement of the lacrimal puncta and were thus classified as having Waardenburg syndrome type 2. The only ocular alterations found were partial heterochromia irides and retinal hypopigmentation. None of the children showed any critical visual deficits.

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