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Heterogeneity in Waardenburg Syndrome

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INTRODUCTION

In 1951, Waardenburg, a Dutch ophthalmologist and geneticist, described a rare autosomal dominant syndrome with the following clinical manifestations, all of which show variable penetrance: (1) dystopia canthorum, a high broad nasal root, and synophrys (confluent eyebrows); (2) pigmentary disorders of the eyes, hair, and skin; and (3) congenital deafness [1]. This disorder, now known as the Waardenburg syndrome, is also called the Klein-Waardenburg syndrome because of a patient described by Klein in 1947 [2] and 1950 [3]. A frequency of 1:40,000 in the Netherlands [1] and 1:20,000 in Kenya (East Africa) [4] has been reported. Prior to the first description of this disorder in 1951 [1], 60 patients had been reported with similar symptoms [2, 3, 6, 8, 58–77]; with the 1,225 others subsequently described, there are 1,285 patients reported in the current literature [1–218].*

In 1971, Arias [5] suggested possible heterogeneity of the syndrome. In the present paper, we investigate this heterogeneity, in particular as it relates to the varying penetrance of deafness (the most serious anomaly associated with the syndrome), by reviewing the literature and information on 34 previously undescribed patients from the Netherlands.

REVIEW OF 1,285 PATIENTS FROM THE LITERATURE

The Syndrome With and Without Dystopia Canthorum

Dystopia canthorum [6] is characterized by a lateral displacement of the medial canthi when the distances between the pupils (fig. 1) and between the lateral canthi are abnormal. This leads to both a shortening of the palpebral fissures in the horizontal direction (blepharophimosis) and a reduced visibility of the medial parts of the sclerae. The inferior lacrimal puncta are also displaced laterally and are situated in front of the cornea. For a positive diagnosis of dystopia canthorum, it is necessary to know the ranges of normal interocular distances. One of the most extensive studies of normal interocular distances was reported by Jöhr [7].

On the basis of the presence or absence of dystopia canthorum, Arias [5] divided the Waardenburg syndrome into three distinct types: type I, with dystopia canthorum; type

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* An appendix containing a complete record of all the cases of Waardenburg syndrome reported in the literature from 1873 through 1975 is available on request from the authors.

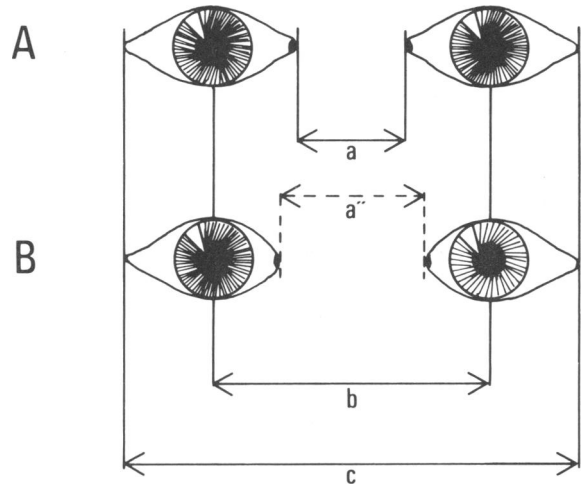

FIG. 1.—Interocular distances used to define dystopia canthorum. *A*, Normal situation; *B*, dystopia canthorum: only increased distance between the medial canthi (a''); *a*, distance between medial canthi; *b*, distance between pupils; *c*, distance between lateral canthi.

II, without dystopia canthorum; and type III or "pseudo-Waardenburg" syndrome, without dystopia canthorum but with a one-sided ptosis. Since type III was described in only two patients, both from the same family [5], it is perhaps premature to establish a "pseudo-Waardenburg" syndrome until more patients fitting this picture are found. Because Arias proved that no parent showing one or more signs of the syndrome including dystopia canthorum produced affected offspring without dystopia canthorum, a division of Waardenburg syndrome into type I and type II seems justified. Thus, genetic heterogeneity seems probable.

Penetrance of Type I and Type II Characteristics

Penetrance of each of the characteristics of the syndrome was calculated using data from the literature provided (1) the family members of a patient were investigated and (2) accurate data on the interocular distances was described. In this way, two groups—276 patients with type I [1, 5, 8–29] and 159 patients with type II [1, 17, 30–52]–were selected for further analysis. Penetrance of each characteristic was calculated for both groups and is given in table 1. Most significantly it was noted that deafness occurs in about one-fourth of the patients with type I and in about half of the patients with type II.

This difference in frequency has important consequences for genetic counseling. Because the mode of inheritance for both types of the syndrome is autosomal dominant, the chance of deafness for a child of a type I patient is about 1 in 8 and for children of a type II patient, about 1 in 4.

Associated Anomalies

A facial cleft (cheilo-, gnatho-, and/or palatoschizis) was reported in 11 (1%) of 1,142 patients described since 1951. In the Netherlands, about 1 in 700 (0.14%)

TABLE 1

PENETRANCE OF THE CHARACTERISTICS OF THE WAARDENBURG SYNDROME TYPE I (WITH DYSTOPIA CANTHORUM) AND TYPE II (WITHOUT DYSTOPIA CANTHORUM)

Characteristics	276 Patients with Dystopia Canthorum in the Literature	31 Patients with Dystopia Canthorum in the Netherlands	159 Patients without Dystopia Canthorum in the Literature
Dystopia canthorum	99	100	0
High, broad nasal root	78	100	29
Synophrys	68	100	23
Heterochromia iridum	31	42	31
Hypoplastic, blue irides	9	13	15
White forelock	33	26	39
Early greying	9	23	6
Partial albinism (skin)	7	23	15
Deafness, bilateral	28	13	53
Deafness, unilateral	8	19	4

NOTE.—Nos. = percentages. Probands are included in the calculations of penetrance.

children were born with a facial cleft [53]; similar frequencies have been given for other countries. It therefore appears that a facial cleft is about eight times as frequent in patients with Waardenburg syndrome than in the general population ($P < .0001$).

Since 1951, chromosomal analysis in 36 patients has been described [16, 19, 20, 29, 144, 154, 159, 161, 172, 181, 186, 199, 204–206], but no structural or numerical aberrations of the chromosomes have been found.

THIRTY-FOUR NEW PATIENTS IN THE NETHERLANDS

In the Netherlands, five previously undescribed families with Waardenburg syndrome were examined. Families 1, 2, and 3 were found because the proband was deaf; families 4 and 5 were found because of pigmentary disorders of the eyes. In all, 31 members of families 1, 2, and 3 demonstrated dystopia canthorum. Although five died, sufficient information was available from pictures and descriptions by family members to include them in the calculations of penetrance. In families 4 and 5, three patients appeared to have the syndrome without dystopia canthorum.

Patients with the syndrome received an extensive examination, including audiometric, vestibular, radiologic, and ophthalmologic studies. The presence of any two of the three major characteristics of the syndrome (dystopia canthorum, pigmentary anomalies and deafness) make a positive diagnosis of the Waardenburg syndrome possible. For example, synophrys and a high, broad nasal root are common in people without the syndrome; therefore, these two characteristics have little diagnostic value unless they occur with dystopia canthorum or pigmentary disorders.

RESULTS AND DISCUSSION

Pedigrees of the five families presented are shown in figures 2–6. In figures 7 and 8, some typical characteristics of Waardenburg syndrome type I can be seen; figure 9 shows a patient with the syndrome type II. No genealogic relationship was demonstrated among the five families. Table 2 summarizes additional information about these 34

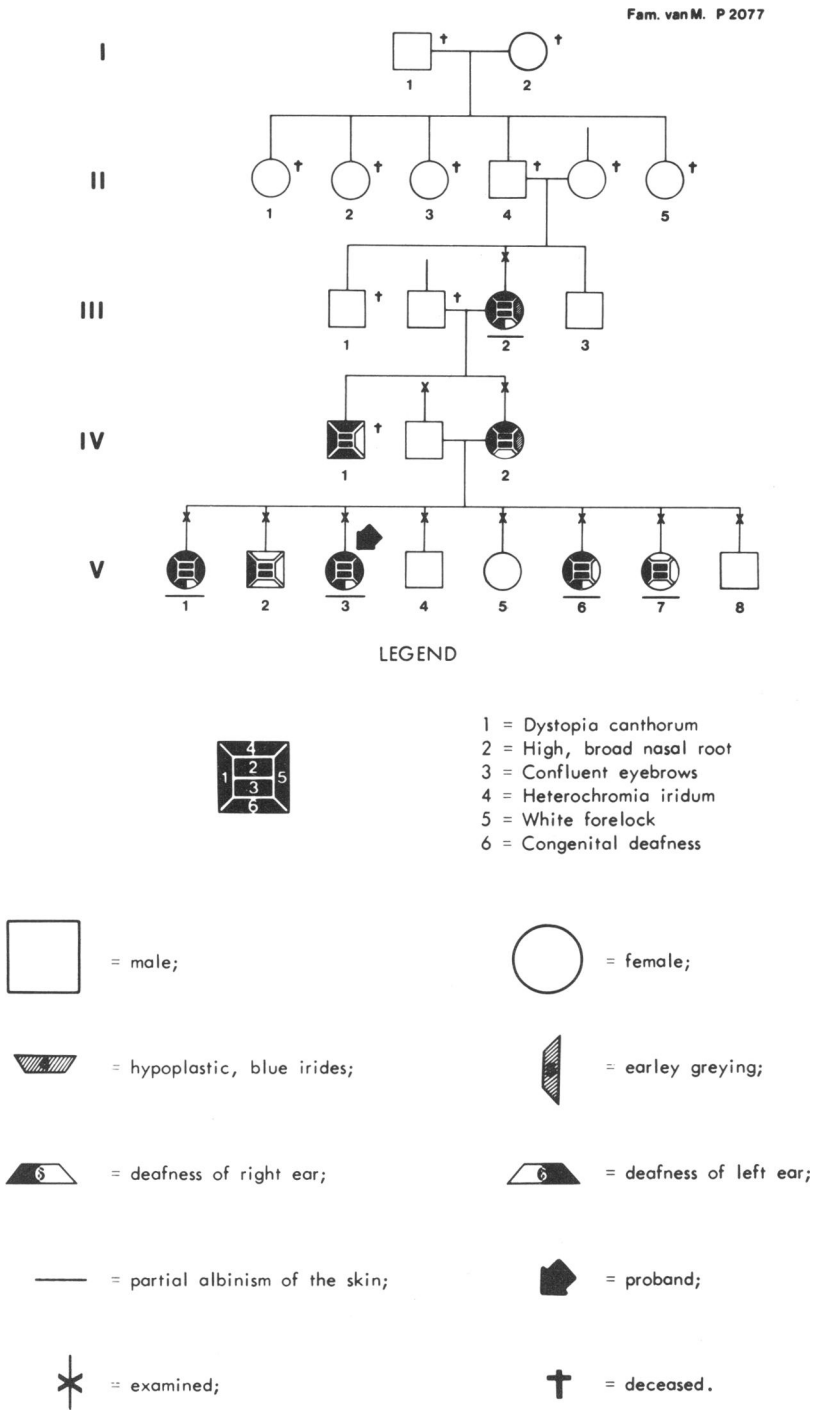

FIG. 2.—Family 1 with Waardenburg syndrome *with* dystopia canthorum (type I).

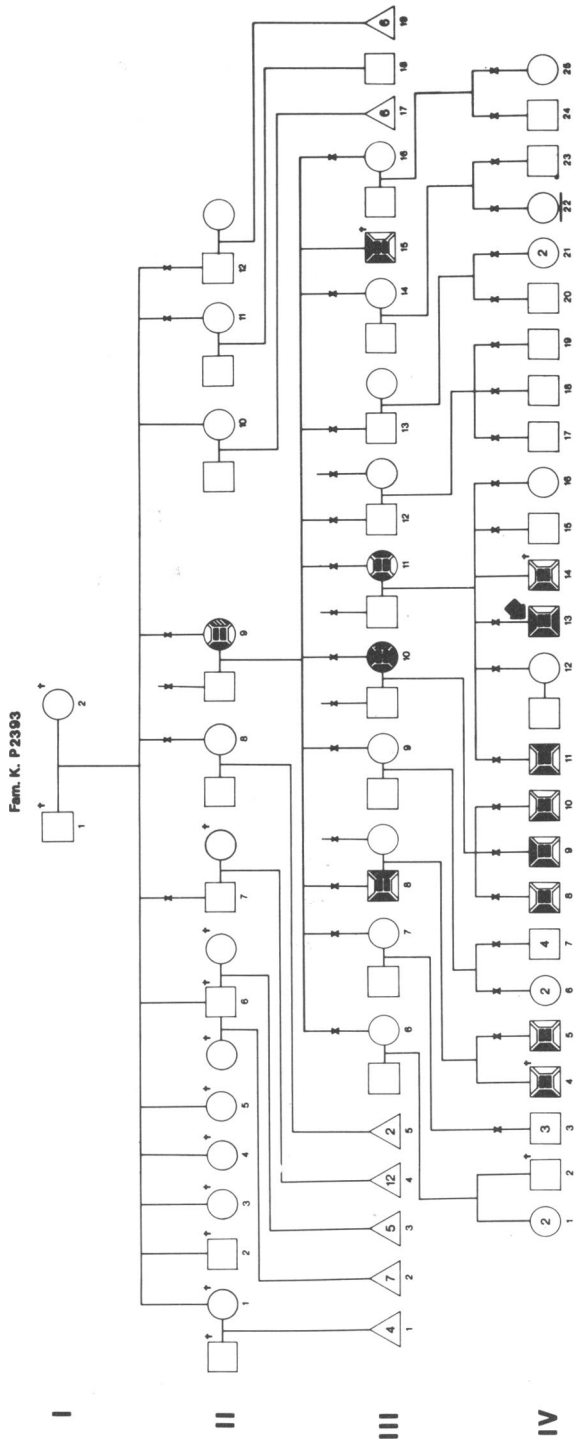

FIG. 3.—Family 2 with Waardenburg syndrome *with* dysopia canthorum (type I). (For explanation of the symbols, see legend to figure 2.)

TABLE 2

34 PATIENTS WITH WAARDENBURG SYNDROME IN THE NETHERLANDS

PATIENTS	SEX	AGE	DISTANCES		
			Between Medial Canthi	Between Pupils	Between Lateral Canthi
Family 1:					
III-2	F	68	45	71	92
IV-1	M	Deceased	...	...	...
IV-2	F	34	45	68	90
V-1	F	15	40	62	82
V-2	M	14	43	63	88
V-3	F	12	44	63	85
V-6	F	8	41	60	85
V-7	F	5	36	56	78
Family 2:					
II-9	F	73	42	67	87
III-8	M	46	46	66	92
III-10	F	41	42	66	87
III-11	F	38	43	63	88
III-15	M	Deceased	...	...	...
IV-4	M	Deceased	...	...	...
IV-5	M	16	44	61	84
IV-8	M	16	42	67	93
IV-9	M	13	42	64	88
IV-10	M	10	37	58	81
IV-11	M	19	44	66	89
IV-13	M	13	40	63	85
IV-14	M	Deceased	...	...	...
Family 3:					
II-4	M	Deceased	...	...	...
III-1	M	74	50	69	93
III-3	M	65	45	64	87
IV-1	M	45	39	63	87
IV-3	M	33	44	66	90
IV-4	M	30	41	63	90
IV-5	F	28	45	63	88
V-2	F	3	37	51	73
V-4	M	3	35	54	76
V-5	F	0	34	45	70
Family 4:					
IV-1	F	7	27	52	75
Family 5:					
V-1	M	20	33	63	90
V-3	F	15	30	61	84

NOTE. — Normal distances between the medial canthi can be found in reference [7]: ≤ 38 mm in adult males; 37 mm in adult females; 36 mm in boys 6–16 years, and 34 mm in girls 6–16 years.

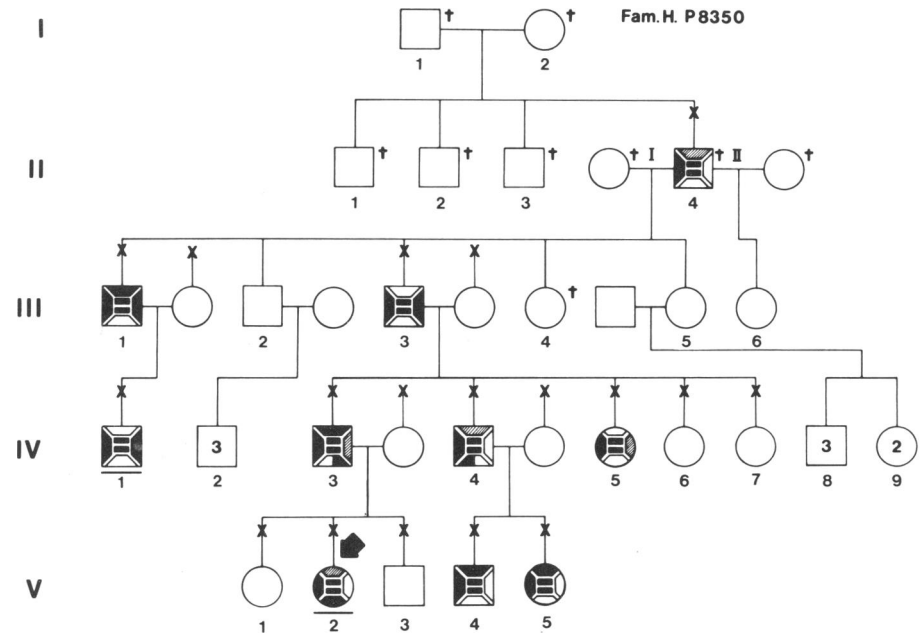

FIG. 4.—Family 3 with Waardenburg syndrome *with* dystopia canthorum (type I). (For explanation of the symbols, see legend to figure 2.)

new patients. The results of the ophthalmologic, audiometric, vestibular, and radiologic studies have been published previously [54–57].

Two patients (V-1 and V-3 of family 1) had an extra nipple under the right mamma. The association of Waardenburg syndrome and polythelia has not been previously described and seems to be fortuitous.

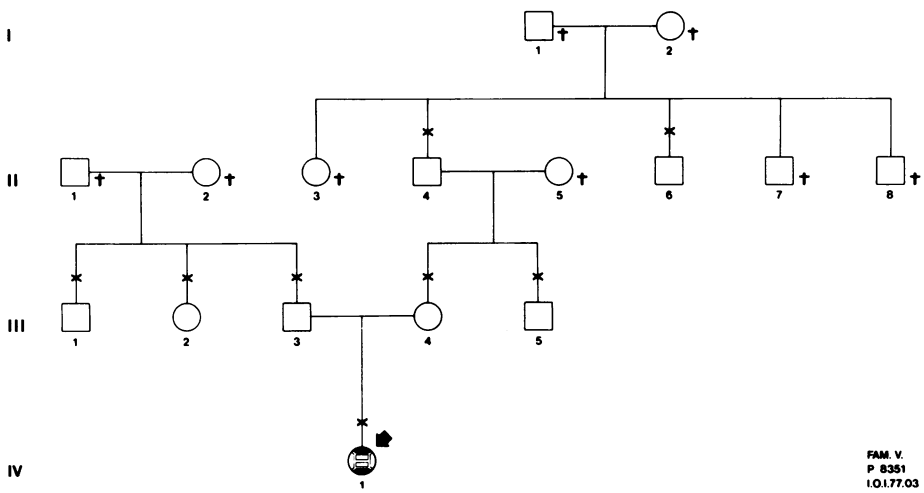

FIG. 5.—Family 4. (For explanation of the symbols, see legend to figure 2.) The proband has Waardenburg syndrome *without* dystopia canthorum (type II).

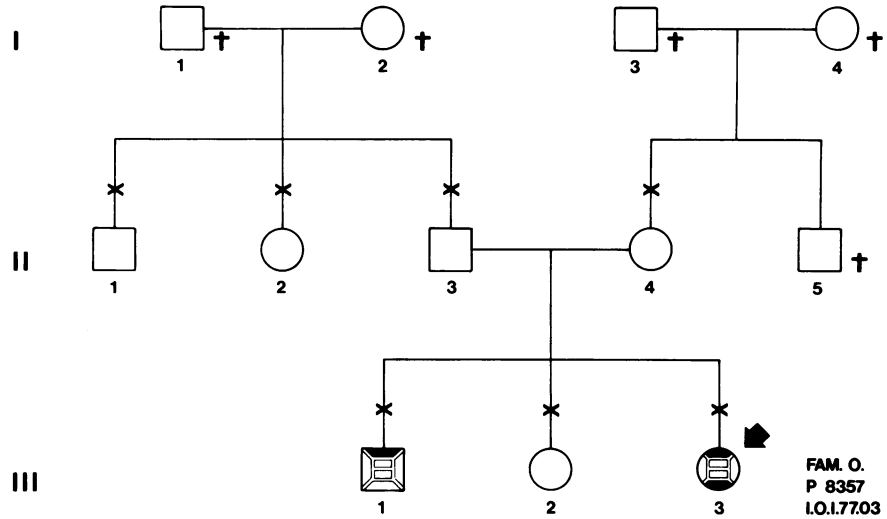

FIG. 6.—Family 5 with Waardenburg syndrome (type II) *without* dystopia canthorum. (For explanation of the symbols, see legend to figure 2).

Inheritance of Type I and Type II

Waardenburg syndrome with dystopia canthorum (type I) appears to be an autosomal dominant disorder in families 1, 2, and 3. The mode of inheritance of type II (without dystopia canthorum) is not clear in families 4 and 5 since only three members exhibit the syndrome. We were unable to find any characteristic typical of the syndrome in the parents of the two affected individuals in family 5. However, both parents did evidence a striking lack of pigmentation in the eyes, hair, and skin; it could be that this represents a minimal expression, as is common in autosomal dominant anomalies.

Regardless, it appears from the review of the literature [1, 7, 30–52] that Waardenburg syndrome type II has an autosomal dominant mode of inheritance. This was confirmed by the four families with 12 individuals suffering from type II found in Kenya (East Africa) [4].

Penetrance of the Characteristics

Out of 77 members of families 1, 2 and 3, 31 show Waardenburg syndrome with dystopia canthorum (type I). Penetrance in these patients was in agreement with the penetrance described in the literature (table 1). Except for the frequency of high, broad nasal root and confluent eyebrows which occurred in 100% of our patients, the other frequencies were in agreement with the literature. Differences which do exist can be explained by the variable criteria for the syndrome; in the literature the characteristics are described either vaguely or not at all. In families 4 and 5, Waardenburg syndrome without dystopia canthorum (type II) is seen in three members; this is too few to calculate the penetrance of characteristics for this type.

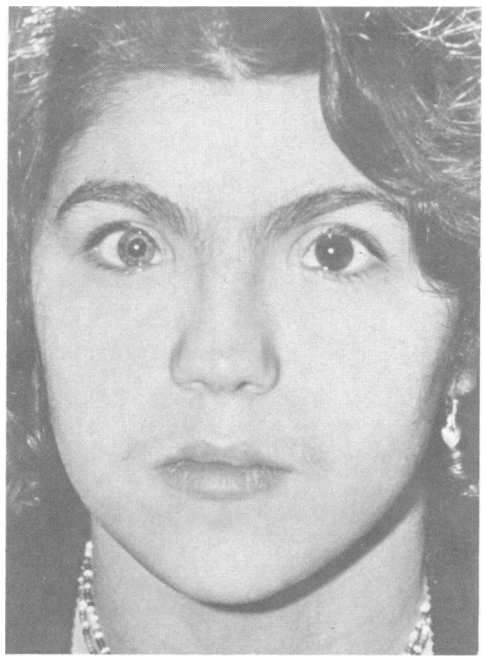

FIG. 7. — A patient with Waardenburg syndrome *with* dystopia canthorum (type I, patient V-1 of family 1).

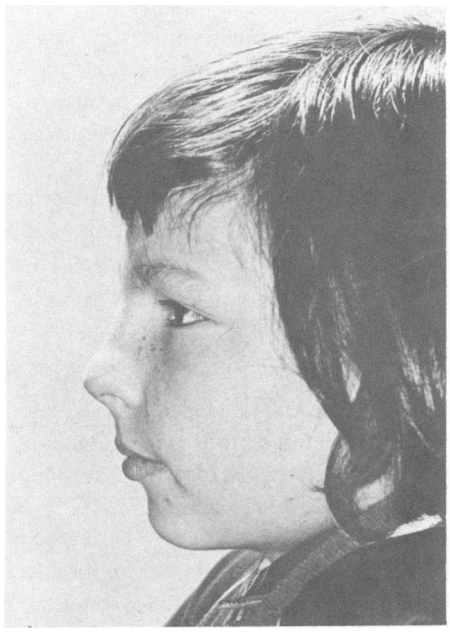

FIG. 8. — A high nasal root with an almost Greek profile as part of the syndrome (patient IV-13 from family 2).

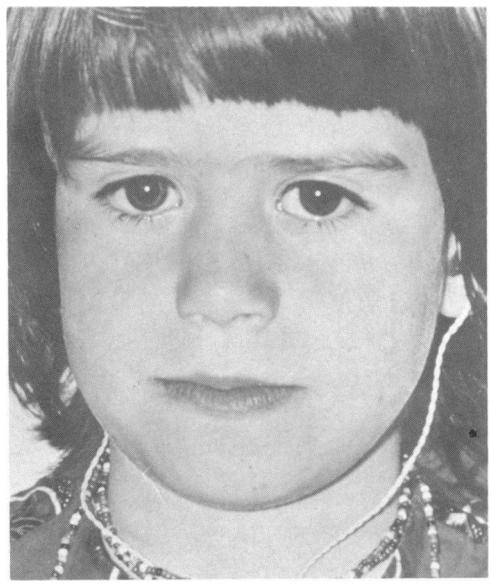

FIG. 9.—A patient with Waardenburg syndrome *without* dystopia canthorum (type II, patient IV-1 from family 4).

SUMMARY

Heterogeneity of Waardenburg syndrome is demonstrated in a review of 1,285 patients from the literature and 34 previously unreported patients in five families in the Netherlands. The syndrome seems to consist of two genetically distinct entities that can be differentiated clinically: type I, Waardenburg syndrome with dystopia canthorum; and type II, Waardenburg syndrome without dystopia canthorum. Both types have an autosomal dominant mode of inheritance.

The incidence of bilateral deafness in the two types of the syndrome was found in one-fourth with type I and about half of the patients with type II. This difference has important consequences for genetic counseling.

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Editor's Note. In 1951 Professor Waardenburg described in the pages of this journal a dominant trait with pleiotropic effects and variable expressivity that has stood the test of time extraordinarily well. The *Journal* takes satisfaction in publishing this updating of Waardenburg syndrome and recognizes with pleasure the dedication of this paper to Professor Waardenburg.

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