

Waardenburg syndrome type II

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Abstract

Waardenburg syndromes are deafness syndromes associated with pigmentary disturbances. Their incidence is 1/270,000 births/year. They are distinguished by their autosomal dominant transmission and their irregular depigmentation. Waardenburg syndrome type II (type IIA when linked to locus 3p13; type IIB when not linked to this locus) is a group of heterogeneous entities distinguished from Waardenburg syndrome type I by the absence of dystopia canthorum. The presence of a family history of congenital deafness or pigmentation anomalies is of importance for the diagnosis. Hearing aids to counter deafness and management of the associated malformations are recommended. Skin and eyes photoprotection is highly recommended.

Keywords

Deafness, pigmentation anomalies, iris heterochromia, *MITF* gene, *SNAI2* gene

Name of the disease and synonyms

Waardenburg syndrome type II (WS II): type IIA (WS2A) when linked to locus 3p13; type IIB (WS2B) when not linked to this locus.

Excluded diseases

[Waardenburg syndrome type I \(WS I\);](#)

[Waardenburg syndrome type III \(WS III\);](#)

[Waardenburg-Shah syndrome;](#)

Other neurocristopathies;

Non-syndromal deafness.

Diagnostic criteria/Definition

WS II is a heterogeneous group of disease that are differentiated from WS I by the absence of dystopia canthorum. The presence of a family history of congenital deafness or pigmentation anomalies is very important for the diagnosis.

Differential diagnosis

Deafness is the most frequent feature of WS II and is more severe than in WS I. Heterochromia of the iris is also more common than in WS I.

Incidence

The incidence has not been estimated, but is less frequent than WS type I.

Clinical description

Clinical features include:

- Neurosensory deafness (71% of the patients);
- Pigmentation anomalies of the eyes (47% of the patients);
- Other pigmentation anomalies, for example white forelock (29%), premature graying of the hair (27%), irregular depigmentation of the skin (15%);
- Absence of facial dysmorphism.

The following W index can be used in order to rule out dystopia canthorum:

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

$$\text{with } X = (2a - 0.2119c - 3.909)/c$$

$$\text{and } Y = 2a - 0.22479b - 3.909/b;$$

(**a** is the internal intercanthal distance, **b** is the interpupillary distance and **c** is the external intercanthal distance). An normal W index is below 1.95.

Management and treatments

The same recommendations as those cited for [WS type I](#): hearing aids and management of the associated malformations. Skin and eyes photoprotection is highly recommended.

Etiology

This syndrome corresponds to a primary abnormality of melanocytes, affecting the eyes, ears, hair and skin. Mutations are found in the microphthalmia-associated transcription factor (*MITF*) gene, located in chromosome 3p13 in 15% of the patients (WS2A). This gene encodes a transcription factor that probably plays a major role in the development of melanocytes.

Genetic heterogeneity has been observed, since the 3p locus has been excluded in different families. In particular, a homozygous deletion in the *SNAI2* gene has been found in 2/38 WS2 patients with no *MITF* mutation (chromosome 8q11, WS2D), a gene responsible for pigmentary disturbances in mice.

Two other loci have been suggested but should be confirmed: chromosome 1p21-p13.3 (WS2B) and chromosome 8p23 (WS2C).

Molecular diagnosis

Search for a mutation in the *MITF* gene is possible but it will only be found in a small percentage of cases.

Genetic counselling

The syndrome is transmitted following an autosomal dominant inheritance with variable inter- and intrafamilial expressivity. Search for a mutation in the *MITF* gene mutations can be helpful for genetic counselling in some cases.

Prenatal diagnosis

Prenatal diagnosis is possible in the families in which a mutation has been identified, but remains highly controversial for ethical reasons.

Unresolved questions and comments

Mutations in the *MITF* gene were discovered because of the homology with the murine model of microphthalmia, in which affected mice have white fur, hypoplastic and depigmented eyes, osteopetrosis and deafness. The other genes implicated in the disease are currently unknown. *MITF* mutation has also been found in a family with [Tietz-Smith syndrome](#) (deafness and uniform depigmentation).

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