

Waardenburg syndrome type I

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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 I associates at least 2 major or 1 major and at least 2 minor clinical criteria. Major criteria are: dystopia canthorum, pigmentary disturbances (white forelock, eyelashes, eyebrows and body hair; heterochromia of the iris, sapphire blue eyes), cochlear neurosensory deafness, a suggestive family history. Minor criteria include: cutaneous pigmentary anomalies with depigmented zones, synophrys, prominent nasal root, hypoplastic alae nasi, premature graying of the hair. The molecular diagnosis is based on the search for a heterozygous mutation in the paired box-containing, PAX3 gene in chromosome 2q. Hearing aids to counter deafness and management of the associated malformations are recommended. Skin and eyes photoprotection is highly recommended.

Keywords

Pigmentary disturbances, sensorineural hearing loss, dystopia canthorum, PAX3 gene

Name of the disease and synonyms

Waardenburg syndrome type I (WS I)

Excluded diseases

- Other WS:
 - [Waardenburg syndrome type II \(WS II\)](#)
 - [Waardenburg syndrome type III \(WS III\)](#);
 - [Waardenburg–Shah syndrome](#);
 - Other neurocristopathies:

- [piebald trait](#) (isolated or associated with deafness and/or ataxia);
- [vitiligo](#) (isolated or associated with deafness and/or achalasia);
- BADS syndrome (black locks–albinism–deafness syndrome);
 - Non-syndromal deafness.

Diagnostic criteria/Definition

WS are deafness syndromes associated with pigmentary disturbances. They are distinguished by their autosomal dominant transmission and their inhomogeneous depigmentation.

WS I associates at least 2 major or 1 major and 2 minor criteria listed below.

Differential diagnosis

Presence of a lateral displacement of the inner canthus of each eye in WSI vs WSII (*MITF* heterozygous mutations).

Other features that are more frequent in WSI than in WSII: synophrys, white forelock, leukoderma and nasal root hyperplasia. Hearing impairment and iris pigmentation disturbances are less frequent in WSI than in WSII.

Absence of limb anomalies in WSI vs WS III (*PAX3* heterozygous or homozygous mutations).

Incidence

The annual incidence for WS of all types is 1/270,000 births. WS comprises about 3% of congenitally deaf children.

Clinical description

Major clinical criteria

- Dystopia canthorum (lateral displacement of the inner canthus of each eye), the most consistent sign, is found in 98% of the patients.

The dystopia canthorum must meet strict clinical criteria and not be confused with hypertelorism. The following W index can be used:

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

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

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

(*a* is the internal intercanthal distance, *b* is the interpupillary distance and *c* is the external intercanthal distance).

W index greater than 1.95 is considered abnormal. Previously, W index greater than 2.07 was necessary to diagnose WSI in individuals meeting all the other diagnostic criteria, but molecular analyses of the *PAX3* gene reduced the index value of greater than 1.95.

- Pigmentation abnormalities: a white forelock can be present at birth and is found more often in the other types (penetrance 43-48%). The white forelock can be present at birth or appear later, and may become normally pigmented over time. Eyebrows, eyelashes and body hair can be depigmented. Heterochromia of the iris and/or sapphire blue eyes can be present (penetrance 15-31%).

- Neurosensory cochlear deafness with loss of more than 25 dB for at least 2 frequencies between 250 and 4000 Hz is present in 58% of the patients. Hearing loss is typically non progressive, either unilateral or bilateral. The most common type is bilateral profound loss > 100 db.
- An autosomal dominant family history is suggestive of the disease.

Minor clinical criteria

- Cutaneous depigmented zones (penetrance 30-36%)
- synophrys
- prominent nasal root (penetrance 52-100%)
- hypoplastic alae nasi
- premature graying of the hair (penetrance 23-38%)

Rare signs that have been reported

- Sprengel anomaly (congenital elevation of the scapula)
- Spina bifida
- Uni- or bilateral cleft lip and/or palate
- Congenital cardiac malformation
- Abnormal vestibular function

Management including treatment

Hearing aids and management of the associated malformations are recommended.

Etiology

This syndrome is secondary to the absence of melanocytes in the skin, hair, eyes and the stria vascularis ductus cochlearis (stratified epithelium lining the upper part of the ligamentum spirale cochleae). The melanocytes are a normal component of the inner ear. This disease is a consequence of abnormal migration of cells derived from the neural crest.

An heterozygous mutation in the paired box-containing, *PAX3* gene localized to chromosome 2q37 is responsible for the phenotype. It contains 10 exons, with the presence of a paired box in exons 2-4 and a homeobox in exons 5-6. To date, more than 50 mutations have been identified. They vary widely from one family to another and often cover the entire gene. Mutations within the gene or deletions of the entire gene result in haploinsufficiency of *PAX3*. A genotype-phenotype correlation has been difficult to demonstrate: deletions involving the entire gene can give rise to a phenotype similar to that caused by a single base pair mutation; moreover, two single base pair mutations of the same type and the same region can generate very different phenotypes. The absence of

genotype–phenotype correlations suggests that modifier genes probably intervene.

Molecular diagnosis

The molecular diagnosis relies on the search for a heterozygous mutation in the *PAX3* gene. Over 90% of disease-causing mutations are detected by direct sequencing.

Genetic counselling

This syndrome is inherited as an autosomal dominant trait with a large inter- and intrafamilial expressivity. The features can range from simple dystopia of the canthi to the complete clinical picture. *De novo* mutations are also possible but rare.

Prenatal diagnosis

Prenatal diagnosis is possible when the familial mutation is known but not justified, since there is no impairment of intellectual function or lifespan.

Unresolved questions and comments

Heterozygous *PAX3* mutations have also been found in patients with [craniofacial-deafness-hand syndrome](#), in which individuals have a flat profile, ocular hypertelorism, hypoplastic nose with slit-like nares and sensorineural hearing loss. X-ray findings include a small maxilla, absent or small nasal bones and ulnar deviation of the hands.

An interaction has been shown between *PAX3*, *SOX10* and *MITF* in the regulation of melanocyte development.

The animal model is the Splotch mouse, in which mutations in the *pax3* gene on chromosome 1 have been found, the murine homologue of the region implicated on human chromosome 2. This gene encodes for a DNA-binding protein containing a homeodomain, early expressed during neurogenesis. *Pax3* is found in neural tube cells with mitotic activity, spinal ganglia and certain cells involved in craniofacial

development, the mesenchyme of the limbs but not in melanocytes. The heterozygous Splotch mouse has white fur on its abdomen, sometimes also on its feet, back and/or tail, and some of them are deaf. The homozygous Splotch mouse has a malformation of the internal ear and lethal malformations of the neural tube.

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