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Cancer Prone Disease Section

Review

Waardenburg syndrome (WS)

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Identity

Alias

Klein-Waardenburg syndrome (WS3)
Waardenburg syndrome with upper limb anomalies (WS3)
White forelock with malformations (WS3)
Waardenburg-Hirschsprung disease (WS4)
Waardenburg syndrome variant (WS4)
Shan-Waardenburg syndrome (WS4)
Hirschsprung disease with pigmentary anomaly (WS4)

Note

Waardenburg syndrome (WS) is an auditory-pigmentary syndrome caused by a deficiency of melanocytes and other neural crest-derived cells.
The disease was named for Petrus Johannes Waardenburg, a Dutch ophthalmologist (1886-1979) who was the first to notice that people with two different coloured eyes frequently had hearing problems.

Inheritance

Inherited in an autosomal dominant manner with an incidence of 1 in 40 000 newborns. Almost 90% of patients have an affected parent but the symptoms in the parent can be quite different from those in the child.

Clinics

Note

Waardenburg syndrome (WS) is a hereditary auditory-pigmentary syndrome, the major symptoms being congenital sensorineural hearing
loss and pigmentary disturbance of eyes, hair and skin. Depending in additional symptoms, WS can be classified into four types: WS type I (WS1) is associated with facial deformity such as dystopia canthorum (lateral displacement of the inner canthi); WS2 has no other symptoms; WS3 is associated with upper limb deformity; and WS4, with megacolon.

Phenotype and clinics

Disease with variable penetrance and several know clinical types. Characteristics may include depigmentation of the hair and skin, congenital deafness, heterochromia iridis, medial eyebrow hyperplasia, hypertrophy of the nasal root, and especially dystopia canthorum. The underlying cause may be defective development of the neural crest (neurocristopathy). Waardenburg's syndrome may be closely related to piebaldism. Klein-Waardenburg syndrome refers to a disorder that also includes upper limb abnormalities.

Neoplastic risk

Slight increased risk for rhabdomyosarcoma.

Treatment

No specific treatment is available for Waardenburg syndrome. Attention must be paid to any hearing deficit and hearing aids and appropriate schooling may need to be provided. Type 4 patients with constipation require special attention to their diet and medications to keep their bowels moving.

Prognosis

With correction of hearing deficits, affected people should be able to lead a normal life.

Genes involved and proteins

Note

WS can be classified into for types. At least one gene responsible for each type of WS has been cloned and for these cloning procedures mice with pigmentation

anomalies have contributed greatly. Six genes contributing to this syndrome- PAX3, SOX10, MITF, SLUG, EDN3 and EDNRB- have been cloned so far, all of them necessary for normal development of melanocytes.

PAX3

Location
2q35-q37

Note
PAX3 is an important gene in muscle development and muscle-producing neoplasms such as rhabdomyosarcomas.

DNA/RNA
Description: 10 exons.

Protein
Description: 206-215 residues.
Expression: is expressed during embryonic development. Skeletal muscle, esophagus, cerebellum, pancreas, liver and stomach.
Function: Transcription factor.

Mutations
Mutations in PAX3, which encodes a paired homeodomain transcription factor, are responsible for Waardenburg syndrome 1 and 3.
PAX3 was shown to bind and transactivate the MITF promoter, thereby demonstrating the role of PAX3 in the regulation of MITF expression. This observation supports an epistatic relationship between MITF and PAX3 and can explain the pigmentary disorders observed in WS1 and 3, because MITF controls melanocyte development. PAX3 defects affect neural crest cell derivatives, resulting in the presence of craneofacial malformations.

SOX10

Location
22q13

DNA/RNA
Description: 5 exons.

Protein

SOX10, a protein that modulates other transcription factors (including PAX3) belongs to the high mobility group (HMG) box superfamily of DNA-binding proteins. It is first expressed during development in cells of the neural crest that contributes to the forming peripheral nervous system, and can be detected in the sensory, sympathetic and enteric ganglia and along nerves. SOX10 is also transiently expressed in melanoblast.
Description: 466 residues.
Expression: During development in cells of the neural crest.
Function: Transcription factor.

Mutations
Mutations in Sox10 also result in WS4.
How mutations in this gene lead to deafness and pigmentary abnormalities, shared by all the WS subtypes, was not elucidated. It was tempting to propose that the WS4 genes are directly or indirectly involved in the regulation of MITF expression that is crucial for melanocyte development.
SOX10 binds and transactivates the MITF promoter, whereas Sox10 mutants found in WS4 patients failed to stimulate the MITF promoter. Thus, there is an epistatic relationship between SOX1 and MITF, thereby giving a molecular basis for the audio-pigmentary defect in patients with WS4.
SOX10 joins Pax3, CREB and LEF1 in the list of transcription factors that control MITF expression.

GENE	Syndrome	Specific symptoms
PAX3	WS1; WS3	Dysthopia canthorum, hypoplasia of limb muscle; contracture of elbows, fingers.
MITF	WS2	Main symptoms only (auditory-pigmentary syndrome)
SLUG	WS2	Main symptoms only (auditory-pigmentary syndrome)
EDNRB	WS4	Hirschsprung's disease
EDN3	WS4	Hirschsprung's disease
SOX10	WS4	Hirschsprung's disease

Table 1: Genes involved in Waardenburg syndrome (WS).

MITF

Location
3p14.1-p12.3

DNA/RNA
Description: 9 exons.

Protein
Microphtalmia-associated transcription factor (MITF) is a basic helix-loop-helix, leucin zipper transcription factor that plays a pivotal role in survival and differentiation of melanocytes, the cells that produce melanin pigments. MITF has been demonstrated to up-regulate the expression of the genes involved in melanin synthesis, such as tyrosine, TRP1, and TRP2. Further MITF is thought to be a master gene in melanocyte differentiation, because its forced expression in fibroblast leads to the expression of melanocytes-specific enzymes required for melanin synthesis.
Description: 520 residues.
Expression: in melanocytes.
Function: Transcription factor.

Mutations
In humans, mutations, of MITF are responsible for Waardenburg syndrome (WS) type 2, characterized by pigmentation abnormalities and sensorineural deafness due to the absence of melanocytes from the stria vascularis of the inner ear.
In mice, mutations in the microphthalmia gene cause pigmentation disorders because of the absence of melanocytes, supporting the involvement of MITF in melanocyte survival.
Over 20 different Mitf mutations have been described in mice. They all result in a deficiency in skin or coat melanocytes ranging in severity from minor pigmentary defects with normal eyes to total lack of coat and eye pigmentation, small colobomatous eyes, deafness and in some instances osteopetrosis.

SLUG

Location
8q11.21

DNA/RNA
Description: 3 exons.

Protein
SLUG a zinc finger transcription factor is a marker of neural crest cells in Xenopus, zebrafish and chick embryos and probably has a functional role in formation of premigratory neural crest. In the mouse, the corresponding gene, Slugh, is expressed in migratory but not premigratory neural crest cells and is not essential for neural crest development.
Description: 268 residues.
Expression: Placenta, adult heart, pancreas, liver, kidney and skeletal muscle.
Function: Transcriptional repressor.

Mutations
Mice lacking Slugh have patchy deficiency of melanocytes, a phenotype similar to human Waardenburg syndrome. It has been shown that some human patients with Waardenburg syndrome carry homozygous deletions of SLUG as their only detected genetic abnormality, thus defining a recesive form of type 2 WS. Preliminary investigations of the role of SLUG in melanocyte development show that it is a downstream target of MITF, which acts on an E-box sequence in the SLUG promoter.

EDN3 (ENDOTHELIN 3)

Location
20q13.2-q13.3

DNA/RNA
Description: 5 exons.

Protein
Description: 230 residues.
Expression: Trophoblasts, placental stem villi vessels.
Function: Peptide hormone.

EDNRB (ENDOTHELIN RECEPTOR, TYPE B)

Location
13q22

DNA/RNA
Description: 7 exons.

Protein
Description: 442 residues.
Expression: lung, placenta, kidney and skeletal muscle.
Function: G protein-coupled receptor.

Mutations
WS4 is also caused by mutations in endothelin B receptor or in endothelin 3. How mutations in these genes lead to deafness and pigmentary abnormalities, shared by all the WS subtypes, was not elucidated. It was tempting to propose that the WS4 genes are directly or indirectly involved in the regulation of MITF expression that is crucial for melanocyte development.

To be noted

Mouse models
Mutant mice with coat color anomalies were helpful in identifying these genes, although the phenotypes of these mice did not necessarily perfectly match those of the four types of WS. There are several mice with mutations of murine homologs of WS genes and verify their suitability as models for WS with special interest in the cochlear disorder. The mice include splotch (Sp), microphthalmia (mi), Slugh -/-, WS4, JF1, lethal-spotting (ls), and Dominant megacolon (Dom).

***splotch (Sp)* mice as a model for WS1**

The mouse Pax3 gene was identified as the gene responsible for splotch (Sp) mice. Sp mice exhibit a number of characteristic developmental anomalies which predominantly affect the neural tube and neural crest. Severe alleles in six types of homozygous Sp mice are fatal at the embryonic stage, and even splotch-retarded (Spd) mice, which have the least severe allele, encoding Pax3 with a substitution mutation at the paired domain, die at birth. Heterozygous Sp (Sp/+) mice survive after birth and have white belly spots, but curiously, showed no sign of auditory defects; WS1 patients are usually heterozygous at the PAX3 gene and yet many show auditory dysfunction. The phenotype of Spd mice varies depending on their genetic background, suggesting the existence of modifier genes. It has been estimated that at least two genes interact with Spd to influence the craniofacial features.

***microphthalmia (mi)* mice as a model for WS2**

Homozygous mi mice are microphthalmic due to the loss of retinal pigmentary epithelial (RPE) cells, white in coat color due to the loss of melanocytes, and deaf.
11 types of mi gene mutations, so far identified in mi mice, are transmitted in either a recesive or semi-dominant manner. In contrast, in humans is transmitted in a dominant manner.

***Slugh-/-* mice as a model for WS2**

Slugh-/- mice have diluted coat color, a white forehead blaze, and areas of depigmentation on the ventral body, tail and feet. Hearing function has not yet been assessed in Slugh-/- mice, but hyperactivity and circling behaviours observed in some Slugh-/- mice suggest a vestibule-cochlear disorder.

***WS4* mice as a model for WS4**

Homozygous WS4 mice showed pigmentation anomaly (white coat color with black eye), aganglionic megacolon and cochlear disorder. Exons 2 and 3, which encode transmembrane domains III and IV of the Ednrb G-protein-coupled receptor protein, were deleted in these mice. Cochlea of WS4 mice showed endolymphatic collapse, due to the lack of melanocytes (intermediate cells) in the stria vascularis.

***JF1* mice as a model for WS2**

The JF1 mice are an inbred strain of mice derived from Japanese wild mice, which are often bred by Japanese laymen as fancy „panda¾ mice because of their cute appearance with black eyes and white spotting on a black coat. JF1 mice are not lethal even in the homozygous state. This non-lethality of JF1 mice is probably due to the fact that the mutation in mice is an insertional mutation in intron 1 that creates a cryptic splicing acceptor site that results in decreased expression of wild-type Ednrb but does not cause aganglionic megacolon. As JF1 mice have pigmentation anomalies and hearing impairment- but not megacolon or dysmorphogenesis- they constitute a mouse model of WS2. These notions are consistent with the finding that WS2 is occasionally caused by mutations in EDNRB.

***lethal-spotted (ls)* mice as a model for WS4**

Homozygous mutations of the endothelin 3 (EDN3) gene cause coat spotting and aganglionic megacolon in ls mice and gene targeted edn3 null mice. Some of these mice can survive and mate; they are potentially a model for WS4, although cochlear disorders of these mice remain to be examined.

***Dominant megacolon (Dom)* mice as a model for WS4**

The Sox10 gene is mutated in the dominant megacolon (Dom) mouse, an animal model of neurocristopathy, whose phenotype is reminiscent of Waardenburg-Hirschsprung patients. The pigmentary phenotype also suggests that Sox10 expression is essential for melanocyte development.
Homozygous Dom mice are lethal and their embryos lack neural crest-derived cells expressing the melanocyte lineage markers. Heterozygous Dom mice show white spotting and some of them show megacolon. Dom mice not respond to sound. They did not show endolymphatic collapse, suggesting that their stria vascularis had intermediate cells (melanocytes) sufficient for normal production of endolymph. However, their organ of Corti was missing.

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