Waardenburg-Shah Syndrome

Alternative Names
Waardenburg Syndrome, Type IV
WS4
Waardenburg-Hirschsprung Disease
Waardenburg Syndrome Variant
Shah-Waardenburg Syndrome
Hirschsprung Disease with Pigmentary Anomaly

WHO International Classification of Diseases
Congenital malformations, deformations and chromosomal abnormalities

OMIM Number
277580

Mode of Inheritance
Autosomal recessive

Gene Map Locus
22q13, 20q13.2-q13.3, 13q22

Description
Waardenburg-Shah syndrome is a disorder that occurs in all races, with reports from Netherlands, India, and other countries. Hirschsprung disease (HSCR) is a multigenic neurocristopathy clinically recognized by aganglionosis of the distal gastrointestinal tract. The association of Waardenburg’s syndrome and Hirschsprung disease can be explained by the occurrence of migration of cells from the embryonic neural crest to produce melanocytes, the adrenal ganglia, sympathetic ganglia, and sensory components of the spinal and cranial nerves. Since neural crest cells also migrate to the visceral ganglia of the gastrointestinal tract, it is possible that pigmentary anomalies could be associated with anomalies of the ganglion cells in the viscera.

Waardenburg-Shah syndrome is divided into four distinct types on the basis of absence or presence of dystopia canthorum. Type I with dystopia canthorum, type II without dystopia canthorum, and type III or “pseudo-Waardenburg” syndrome, without dystopia canthorum but with a one-sided ptosis. Patients presenting with aganglionosis in association with hypopigmentation are classified as Waardenburg syndrome type 4 (Waardenburg-Shah syndrome, WS4).

Molecular Genetics
Waardenburg-Shah syndrome depends on a polygenic gene which is transmitted regularly or irregularly as an autosomal dominant trait with variable penetrance and expressivity. The penetrance of the feature-dystopia canthorum ranges from 76-99%. Variability in the disease phenotype of Waardenburg-Shah syndrome patients with equivalent mutations suggests the influence of genetic modifier loci in this disorder. Waardenburg-Shah syndrome could result from mutations in the endothelin-B receptor gene (EDNRB), in the gene for its ligand, endothelin-3 (EDN3), or in the SOX10 gene.

Epidemiology in the Arab World

Tunisia
In two girls born to consanguineous Tunisian parents, Attie et al. (1995) described features of both Waardenburg syndrome and Hirschsprung disease. Neither affected sister had dystopia canthorum. However, both had deafness, white forelock, and heterochromia iridis, as well as Hirschsprung disease. One year later, Bonnet et al. (1996) reported a Tunisian infant of consanguineous parents with pigmented disorders, congenital deafness and long-segment Hirschsprung disease. Her elder sister had the same disorders but with short-segment aganglionosis. Their father, mother and two brothers are healthy without history of deafness, constipation or pigmentary disorder. Bonnet et al. (1996) confirmed that this Waardenburg-Hirschsprung association seems to be a distinct
clinical entity with a possible autosomal recessive mode of inheritance. Linkage analyses performed in this family support the view that neither the RET locus (candidate for familial dominant Hirschsprung disease) nor the HuP2 locus (candidate for Waardenburg syndrome type I) are involved in the disease phenotype. They also suggested that Waardenburg-Hirschsprung complex is a distinct genetic entity and at least one additional locus altering cranial neural crest cell development is responsible for pleiotropic features observed in this association.

**Oman**

Abdulrazzaq (1989) reported a full term baby boy with Waardenburg’s syndrome with long segment Hirschsprung’s disease who was born to a non-consanguineous Omani family. At birth the baby was noted to have a white forelock and a hypopigmented area on the forehead. On the second day of life, he developed abdominal distension. Two male siblings who died during the neonatal period had long segment Hirschsprung’s disease, with one of them having in addition, a white forelock.

**United Arab Emirates**

[See also: Oman > Abdulrazzaq, 1989].

**References**


**Contributors**

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