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NLM Citation: Milunsky JM. Waardenburg Syndrome Type I. 2001 Jul 30 [Updated 2017 May 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Waardenburg Syndrome Type I

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Created: July 30, 2001; Revised: May 4, 2017.

Summary

Clinical characteristics

Waardenburg syndrome type I (WS1) is an auditory-pigmentary disorder comprising congenital sensorineural hearing loss and pigmentary disturbances of the iris, hair, and skin, along with dystopia canthorum (lateral displacement of the inner canthi). The hearing loss in WS1, observed in approximately 60% of affected individuals, is congenital, typically non-progressive, either unilateral or bilateral, and sensorineural. Most commonly, hearing loss in WS1 is bilateral and profound (>100 dB). The majority of individuals with WS1 have either a white forelock or early graying of the scalp hair before age 30 years. The classic white forelock observed in approximately 45% of individuals is the most common hair pigmentation anomaly seen in WS1. Affected individuals may have complete heterochromia iridium, partial/segmental heterochromia, or hypoplastic or brilliant blue irides. Congenital leukoderma is frequently seen on the face, trunk, or limbs.

Diagnosis/testing

The diagnosis of WS1 is established in most individuals by physical examination for clinical criteria including: sensorineural hearing loss, pigmentary changes in the hair and eyes, dystopia canthorum identified by calculation of the W index, and specific facial features. Identification of a heterozygous *PAX3* pathogenic variant by molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Management of the hearing loss depends on its severity; cochlear implantation has been successfully used in individuals with WS1.

Evaluation of relatives at risk: If the family-specific *PAX3* pathogenic variant is known, molecular genetic testing of relatives at risk allows for early screening of those at risk for hearing loss.

Pregnancy management: Folic acid supplementation in pregnancy is recommended for women at increased risk of having a child with WS1 because of possibly increased risk for neural tube defects in association with WS1.

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Genetic counseling

Waardenburg syndrome type I (WS1) is inherited in an autosomal dominant manner. The majority of probands have an affected parent. A minority of probands do not have an affected parent and are presumed to have WS1 as a result of a *de novo* pathogenic variant. Offspring of an individual with WS1 have a 50% chance of inheriting the pathogenic variant. If the pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing for this disease/gene or custom prenatal testing. Although this testing can determine whether the fetus has inherited the *PAX3* pathogenic variant, it cannot determine the clinical manifestations or their severity.

Diagnosis

Suggestive Findings

Waardenburg syndrome type I (WS1) **should be suspected** in individuals with several of the following major and minor criteria.

Major criteria

- Congenital sensorineural hearing loss
- White forelock, hair hypopigmentation
- Pigmentation abnormality of the iris:
  - Complete heterochromia iridum (irides of different color)
  - Partial/segmental heterochromia (two different colors in same iris, typically brown and blue)
  - Hypoplastic blue irides or brilliant blue irides
- Dystopia canthorum, W index >1.95 (see Note – W index)
- Affected first-degree relative

Minor criteria

- Skin hypopigmentation (congenital leukoderma)
- Synophrys and/or medial eyebrow flare
- Broad/high nasal root, low-hanging columella
- Underdeveloped *alae nasi*
- Premature gray hair (age <30 years)

Note – W index: The measurements necessary to calculate the W index (in mm) are as follows: inner canthal distance (a), interpupillary distance (b), and outer canthal distance (c).

Calculate $X = (2a - (0.2119c + 3.909))/c$

Calculate $Y = (2a - (0.2479b + 3.909))/b$

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

Click here to download a tool (xlsx) for calculating the W index.

Establishing the Diagnosis

The diagnosis of WS1 **is established** in a proband with two major criteria or one major plus two minor criteria (see Suggestive Findings) as proposed by the Waardenburg Consortium [Farrer et al 1992].

Identification of a heterozygous pathogenic variant in *PAX3* by molecular genetic testing (see Table 1) confirms the diagnosis if clinical features are inconclusive.

Molecular genetic testing approaches can include **single-gene testing**, **a multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *PAX3* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *PAX3* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *PAX3*) fails to confirm a diagnosis in an individual with features of WS1. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Waardenburg Syndrome Type I

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PAX3	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	~6% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Pingault et al [2010], Milunsky [2011, unpublished data], Wildhardt et al [2013]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Milunsky et al [2007]. Note: No duplications have been reported.

Clinical Characteristics

Clinical Description

The phenotype of Waardenburg syndrome type I (WS1) is variable even within a family. Liu et al [1995] summarized the penetrance (percentage) of clinical features of WS1 (see Table 2) in 60 individuals with WS1 and 210 affected individuals reported elsewhere in the literature. Newton [2002] reviewed the clinical features of

the Waardenburg syndromes and Tamayo et al [2008] discussed their screening program for Waardenburg syndrome in Colombia, detailing the percentage of each clinical manifestation; percentages similar to those found in the Liu et al [1995] study were documented. However, ascertainment bias was evident, as all 95 affected individuals had hearing loss and were among the institutionalized deaf population in Colombia.

Table 2. Penetrance of Individuals with Waardenburg Syndrome Type I with Characteristic Clinical Findings

Clinical Finding	% of Affected Individuals
Sensorineural hearing loss	47%-58%
Heterochromic irides	15%-31%
Hypoplastic blue irides	15%-18%
White forelock	43%-48%
Early graying	23%-38%
Leukoderma	22%-36%
High nasal root	52%-100%
Medial eyebrow flare	63%-73%

Based on Liu et al [1995], Pardono et al [2003], Tamayo et al [2008]

Hearing loss. The hearing loss in WS1 is congenital, typically non-progressive, either unilateral or bilateral, and of the sensorineural type. The most common type in WS1 is profound bilateral hearing loss (>100 dB). The laterality of the hearing loss shows both inter- and intrafamilial variation.

Various temporal bone abnormalities have been identified in persons with WS1 and hearing loss [Madden et al 2003]. The temporal bone abnormalities include enlargement of the vestibular aqueduct and upper vestibule, narrowing of the internal auditory canal porus, and hypoplasia of the modiolus.

Hair color. The classic white forelock is the most common hair pigmentation anomaly seen in WS1; it may be present at birth, or appear later, typically in the teen years. The white forelock may become normally pigmented over time. The white forelock is typically in the midline but the patch of white hair may also be elsewhere. In evaluating an individual with suspected WS1 without a white forelock, the individual should be asked whether the hair has been dyed. Red and black forelocks have also been described. The majority of individuals with WS1 have either a white forelock or early graying of scalp hair before age 30 years [Farrer et al 1992].

The hypopigmentation can also involve the eyebrows and eyelashes.

Ocular findings. Individuals with WS1 may have a variety of ocular pigmentary manifestations. The most commonly observed are complete or segmental heterochromia or hypoplastic or brilliant blue irides. Iris and choroidal hypopigmentation (sector pattern more than diffuse pattern) has been described [Shields et al 2013]. Visual acuity does not differ from the general population.

Skin pigmentation. Congenital leukoderma (white skin patches) is frequently seen in WS1 on the face, trunk, or limbs. These areas of hypopigmentation frequently have hyperpigmented borders and may be associated with an adjacent white forelock.

Occasional findings identified in multiple families (although too few to determine the percentage occurrence in this disorder):

- Cleft lip and palate
- Spina bifida, a finding that is not surprising given that WS1 is considered a neurocristopathy with *PAX3* being expressed in the neural crest. Kujat et al [2007] described the prenatal diagnosis of spina bifida in a

family with WS1. Lemay et al [2015] reported a *de novo* pathogenic nonsense *PAX3* variant in an individual with myelomeningocele and WS1.
- Vestibular symptoms including vertigo, dizziness, and balance difficulties, even without hearing loss [Black et al 2001]

Otopathology. The otopathology of an individual with WS1 and a *PAX3* pathogenic variant has been described [Merchant et al 2001]. The findings are consistent with defective melanocyte migration or function resulting in defective development of the stria vascularis leading to sensorineural hearing loss.

Genotype-Phenotype Correlations

PAX3. Genotype/phenotype correlations in *PAX3* are not well established except for the p.Asn47His pathogenic variant, which causes WS3 [Hoth et al 1993], and the p.Asn47Lys pathogenic variant described in craniofacial-deafness-hand syndrome [Asher et al 1996]. DeStefano et al [1998] found that the presence of pigmentary disturbances in individuals with WS1 correlated more with *PAX3* pathogenic variants that delete the homeodomain than with missense or deletion pathogenic variants that include the paired domain. No genotype-phenotype correlation for the hearing loss in WS1 has been found.

***PAX3* partial- or whole-gene deletions.** There appears to be no discernable difference in the severity associated with whole- or partial-gene deletions and the clinical spectrum reported for small intragenic *PAX3* pathogenic variants [Milunsky et al 2007].

***PAX3* and *MITF* double heterozygotes (Waardenburg syndrome type I and Waardenburg syndrome type II [WS2] combined phenotype).** Yang et al [2013] reported a family in which one parent had WS1 due to a heterozygous pathogenic variant in *PAX3* and the other parent had WS2 (see Differential Diagnosis) due to a heterozygous pathogenic variant in *MITF*. Their child was heterozygous for both pathogenic variants and had significantly more pigmentary findings (i.e., white forelock, white eyebrows/eyelashes, and leukoderma) than either parent.

Penetrance

WS1 showed penetrance of at least 85% [Preus et al 1983] before the advent of molecular testing. Careful examination of individuals identified on the basis of pedigree analysis as having a *PAX3* pathogenic variant usually reveals subtle findings (minor criteria). Hence, those individuals with an affected first-degree relative should be examined closely as the penetrance is likely almost complete.

Prevalence

It is difficult to quote a figure for the prevalence of WS1 without population-based molecular analysis. The prevalence figures vary from 1:20,000 to 1:40,000, accounting for approximately 3% of congenitally deaf children [Tamayo et al 2008].

Genetically Related (Allelic) Disorders

Germline *PAX3* pathogenic variants also cause the following:

- Waardenburg syndrome type III (WS3) (Klein-Waardenburg syndrome), characterized by a combination of typical WS1 features and hypoplasia or contractures of the limb muscles or joints, carpal bone fusion, or syndactyly [Hoth et al 1993]. In a consanguineous Turkish family, both parents who are heterozygous for the *PAX3* p.Tyr90His pathogenic variant have WS1; their child who is homozygous for the p.Tyr90His pathogenic variant has WS3 [Wollnik et al 2003].

- Craniofacial-deafness-hand syndrome (CDHS) (OMIM 122880), characterized by a flat facial profile, widely spaced eyes, 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 [Sommer & Bartholomew 2003]. Asher et al [1996] identified a missense variant in *PAX3* in individuals with this disorder. CDHS is apparently distinct from both WS1 and WS3. Gad et al [2008] reported a woman who shares some, but not all features of WS3 and CDHS, and who also has abnormal cranial bones (hypoplastic sinuses and small cochlea). Whereas no sequence alteration or whole-gene deletion of *PAX3* was found, partial-gene deletions were not ruled out. The authors suggest genetic heterogeneity even within the CDHS subtype.

Differential Diagnosis

Waardenburg syndrome type I (WS1) needs to be differentiated from other causes of congenital, non-progressive sensorineural hearing loss (see Deafness and Hereditary Hearing Loss Overview) and from other forms of Waardenburg syndrome.

Waardenburg syndrome type II (WS2). WS1 is distinguished from WS2 by the presence in WS1 of lateral displacement of the inner canthi (dystopia canthorum). If the average W index across a family is less than 1.95, the diagnosis is WS2. Sensorineural hearing loss and heterochromia iridum are the two most characteristic features of WS2. Both are more common in WS2 than WS1. White forelock and leukoderma are both more common in WS1 than in WS2 (see Table 3).

- ***MITF*** (OMIM 156845). Heterozygous *MITF* pathogenic variants [Yang et al 2013] have been described in approximately 10%-20% of individuals with WS2. *MITF* pathogenic variants have also been identified in individuals with Tietz syndrome (deafness with uniform hypopigmentation) [Léger et al 2012].
- ***SOX10*** (OMIM 602229). Heterozygous *SOX10* single-nucleotide variants [Iso et al 2008] and deletions [Bondurand et al 2007, Brezo et al 2014] have been described in about 15% of individuals with WS2. Chen et al [2010] indicated that *SOX10* pathogenic variants occurred with a frequency similar to *MITF* pathogenic variants in individuals with WS2 of Chinese ancestry. Temporal bone abnormalities (specifically bilateral agenesis or hypoplasia of the semicircular canals with a cochlear deformity and enlarged vestibule) are also found in individuals with *SOX10* pathogenic variants [Elmaleh-Bergès et al 2013]. Zhang et al [2012] and Chaoui et al [2011] performed functional analysis of *SOX10* pathogenic variants. A frameshift variant showed a dominant-negative effect on wild type *SOX10*, leading to faster protein decay, possibly resulting in a milder WS2 phenotype [Zhang et al 2012].
- ***SNAI2.*** Biallelic *SNAI2* pathogenic variants were reported in two individuals with features overlapping WS2 (OMIM 608890)

Table 3. Comparison of Clinical Features in WS1 and WS2

Clinical Finding	% of Affected Individuals	
	WS1	WS2
Sensorineural hearing loss	47%-58%	77%-80%
Heterochromic irides	15%-31%	42%-54%
Hypoplastic blue irides	15%-18%	3%-23%
White forelock	43%-48%	16%-23%
Early graying	23%-38%	14%-30%
Leukoderma	22%-36%	5%-12%
High nasal root	52%-100%	0%-14%

Table 3. continued from previous page.

Clinical Finding	% of Affected Individuals	
	WS1	WS2
Medial eyebrow flare	63%-73%	7%-12%

Based on Liu et al [1995], Pardono et al [2003], Tamayo et al [2008]

Waardenburg syndrome type IV (WS4). Individuals having a rare combination of pigmentary abnormalities, hearing loss, and Hirschsprung disease have WS4 [Jan et al 2008] caused by pathogenic variants in one of the following genes: *EDNRB* (OMIM 131244), *EDN3* [Ohtani et al 2006] (OMIM 613265), or *SOX10* [Bondurand et al 2007, Sznajer et al 2008] (OMIM 602229).

See Waardenburg syndrome: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Piebaldism (OMIM 172800). Piebaldism has some pigmentary features in common with Waardenburg syndrome. A white forelock is commonly seen along with absent pigmentation of the medial forehead and eyebrows. Absent pigmentation of the chest, abdomen, and limbs is also common. A characteristic feature is hyperpigmented borders surrounding the unpigmented areas. Heterochromia irides and sensorineural deafness are rarely described. This disorder has shown genetic heterogeneity with dominant loss-of-function variants/whole-gene deletions described involving the *KIT* proto-oncogene. Heterozygous pathogenic variants in *SNAI2* have also been implicated as an etiology in some individuals with piebaldism [Sánchez-Martín et al 2003].

Management

Evaluations Following Initial Diagnosis

The following are appropriate:

- Audiology evaluation
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Management of the hearing loss associated with WS1 depends on its severity (see Deafness and Hereditary Hearing Loss Overview). Cochlear implantation has been successful in individuals with WS [Amirsalari et al 2012, de Sousa Andrade et al 2012, Koyama et al 2016].

Surveillance

The hearing loss in WS1 is typically non-progressive. Hence, repeat audiogram would usually not be necessary.

Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk relatives of an affected individual to allow early screening of those at risk for hearing loss. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Physical examination for the clinical features of WS1 and audiology evaluation if the pathogenic variant in the family is not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Folic acid supplementation in pregnancy has been recommended for women at increased risk of having a child with WS1, given the possibly increased risk of neural tube defects in association with WS1 [Fleming & Copp 1998]; however, no human studies have addressed the ideal dose of folic acid to be used during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Waardenburg syndrome type I (WS1) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with WS1 have an affected parent.
- A minority of individuals diagnosed with WS1 do not have an affected parent and are presumed to have a *de novo* pathogenic variant. The mutation rate has been estimated at 0.4 per 100,000 [Waardenburg 1951]. Jones et al [1975] found evidence of advanced paternal age effect in *de novo* pathogenic variants of WS1.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include examination for clinical manifestations of WS1 by: assessing the facial features, calculating the W index, examining the skin and hair for hypopigmentation, and obtaining an audiogram.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (germline mosaicism has been reported [Kapur & Karam 1991]).
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected or has a *PAX3* pathogenic variant, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to sibs of a proband is low.
- If the *PAX3* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Kapur & Karam 1991].

Offspring of a proband

- Each child of an individual with WS1 has a 50% chance of inheriting the pathogenic variant.
- The clinical manifestations in the offspring cannot be predicted and range from mild or subclinical features through the classic phenotype of WS1, including deafness.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being affected.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PAX3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for WS1 are possible. Although such testing can determine whether the *PAX3* pathogenic variant has been inherited, the results of such testing cannot be used to predict clinical manifestations or their severity.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Waardenburg syndrome
- **NCBI Genes and Disease**
  Waardenburg syndrome
- **American Society for Deaf Children (ASDC)**

800 Florida Avenue Northeast
Suite 2047
Washington DC 20002-3695
Phone: 800-942-2732 (Toll-free Parent Hotline); 866-895-4206 (toll free voice/TTY)
Fax: 410-795-0965
Email: info@deafchildren.org; asdc@deafchildren.org
www.deafchildren.org

- **BabyHearing.org**
  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.
  www.babyhearing.org
- **Hereditary Hearing Loss Homepage**
  hereditaryhearingloss.org
- **National Association of the Deaf (NAD)**
  8630 Fenton Street
  Suite 820
  Silver Spring MD 20910
  Phone: 301-587-1788; 301-587-1789 (TTY)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  www.nad.org
- **National Organization of Albinism and Hypopigmentation (NOAH)**
  PO Box 959
  East Hampstead NH 03826-0959
  Phone: 800-473-2310 (toll-free); 603-887-2310
  Fax: 800-648-2310 (toll-free)
  Email: info@albinism.org
  www.albinism.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Waardenburg Syndrome Type I: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

PAX3	2q36.1	Paired box protein Pax-3	Deafness Variation Database - PAX3 PAX3 gene database	PAX3	PAX3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Waardenburg Syndrome Type I (View All in OMIM)

193500	WAARDENBURG SYNDROME, TYPE 1; WS1
606597	PAIRED BOX GENE 3; PAX3

Molecular Pathogenesis

PAX3 is one of a family of nine human *PAX* genes coding for DNA-binding transcription factors that are expressed in the early embryo. The *PAX* genes are defined by the presence of a paired box (128-amino acid DNA-binding domain). In addition, *PAX3* contains a homeobox [Birrane et al 2009].

Gene structure. *PAX3* has a number of transcript variants that encode different isoforms (see Table A, **Gene**). *PAX3* has ten exons, with the paired box in exons 2-4 and the homeobox in exons 5 and 6 [Birrane et al 2009], and encodes paired box protein Pax-3.

Pathogenic variants. Pathogenic variants within *PAX3* or deletion of the entire gene result in haploinsufficiency. Pathogenic variants within *PAX3* causing Waardenburg syndrome type I (WS1) were first described in 1992 [Baldwin et al 1992, Tassabehji et al 1992]. Multiple abnormal variants in different populations [Chen et al 2010, Pingault et al 2010, Wang et al 2010, Matsunaga et al 2013] – including multiple pathogenic variants within *PAX3* causing WS1, WS1 with spina bifida, WS3, and craniofacial-deafness-hand syndrome (CDHS) (OMIM 122880) – have been described (see Clinical Description, Differential Diagnosis, and Genotype-Phenotype Correlations).

Normal gene product. Bondurand et al [2000] showed that an interaction among *PAX3*, *SOX10*, and *MITF* in the regulation of melanocyte development affects a molecular pathway leading to the auditory-pigmentary abnormalities seen in WS. Given the marked variability in expression of phenotypic features among family members having the same pathogenic variant, the potential role of modifier genes may be significant. Sato-Jin et al [2008] further added to this research by demonstrating that *EDNRB* expression was dependent on *MITF*. In addition, they found that *EDN* directly stimulates the expression of melanocytic pigmentation in an *MITF*-dependent fashion.

Abnormal gene product. The paired box protein Pax3 is an essential regulator of muscle and neural crest-derived cell types, including melanocytes. Analysis of *PAX3* pathogenic variants observed in WS1 revealed varying ability of *PAX3* to bind to and regulate reporter genes fused to either the *MITF* or TRP-1 (tyrosinase-related protein 1) promoters [Corry & Underhill 2005]. Hence, Pax3 appears to be able to regulate target genes through alternate modes of DNA recognition that are dependent on the specific pathogenic variants. Corry et al [2008] showed that the subnuclear localization and altered mobility of the mutated Pax3 protein is a key determinant in its dysfunction. Birrane et al [2009] further demonstrated that certain *PAX3* pathogenic missense variants could destabilize the folding of the Pax3 homeodomain, whereas others affect its interaction with DNA. Wu et al [2015] have examined the loading of *PAX3* on mitotic chromosomes in zebrafish and suggest that mutated *PAX3* proteins have dominant negative effects.

Cancer and Benign Tumors

Somatic *PAX3* variants have been observed in alveolar rhabdomyosarcoma. *PAX3* can fuse with *FKHR*, this fusion creating a gain of function that results in alveolar rhabdomyosarcoma [Wang et al 2008]. Individuals with alveolar rhabdomyosarcoma resulting from this mechanism do not have WS1.

References

Published Guidelines / Consensus Statements

American College of Medical Genetics. Statement on universal newborn hearing screening. Available online. 2000. Accessed 2-25-20.

American College of Medical Genetics Genetic Evaluation of Congenital Hearing Loss Expert Panel. Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Available online. 2002. Accessed 2-25-20.

Literature Cited

Amirsalari S, Ajallouyean M, Saburi A, Haddadi Fard A, Abed M, Ghazavi Y. Cochlear implantation outcomes in children with Waardenburg syndrome. Eur Arch Otorhinolaryngol. 2012;269:2179–83. PubMed PMID: 22159916.

Asher JH, Sommer A, Morell R, Friedman TB. Missense mutation in the paired domain of PAX3 causes craniofacial-deafness-hand syndrome. Hum Mutat. 1996;7:30–5. PubMed PMID: 8664898.

Baldwin CT, Hoth CF, Amos JA, da-Silva EO, Milunsky A. An exonic mutation in the HuP2 paired domain gene causes Waardenburg's syndrome. Nature. 1992;355:637–8. PubMed PMID: 1347149.

Birrane G, Soni A, Ladias JA. Structural basis for DNA recognition by the human PAX3 homeodomain. Biochemistry. 2009;48:1148–55. PubMed PMID: 19199574.

Black FO, Pesznecker SC, Allen K, Gianna C. A vestibular phenotype for Waardenburg syndrome? Otol Neurotol. 2001;22:188–94. PubMed PMID: 11300267.

Bondurand N, Dastot-Le Moal F, Stanchina L, Collot N, Baral V, Marlin S, Attie-Bitach T, Giurgea I, Skopinski L, Reardon W, Toutain A, Sarda P, Echaieb A, Lackmy-Port-Lis M, Touraine R, Amiel J, Goossens M, Pingault V. Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. Am J Hum Genet. 2007;81:1169–85. PubMed PMID: 17999358.

Bondurand N, Pingault V, Goerich DE, Lemort N, Sock E, Caignec CL, Wegner M, Goossens M. Interaction among SOX10, PAX3 and MITF, three genes altered in Waardenburg syndrome. Hum Mol Genet. 2000;9:1907–17. PubMed PMID: 10942418.

Brezo J, Lam C, Vilain E, Quintero-Rivera F. Phenotypic variability in Waardenburg syndrome resulting from a 22q12.3-q13.1 microdeletion involving SOX10. Am J Med Genet Part A. 2014;164A:1512–9. PubMed PMID: 24715709.

Chaoui A, Watanabe Y, Touraine R, Baral V, Goossens M, Pingault V, Bondurand N. Identification and functional analysis of SOX10 missense mutations in different subtypes of Waardenburg syndrome. Hum Mut. 2011;32:1436–49. PubMed PMID: 21898658.

Chen H, Jiang L, Xie Z, Mei L, He C, Hu Z, Xia K, Feng Y. Novel mutations of PAX3, MITF, and SOX10 genes in Chinese patients with type I or type II Waardenburg syndrome. Biochem Biophys Res Commun. 2010;397:70–4. PubMed PMID: 20478267.

Corry GN, Hendzel MJ, Underhill DA. Subnuclear localization and mobility are key indicators of PAX3 dysfunction in Waardenburg syndrome. Hum Mol Genet. 2008;17:1825–37. PubMed PMID: 18325909.

Corry GN, Underhill DA. Pax3 target gene recognition occurs through distinct modes that are differentially affected by disease-associated mutations. Pigment Cell Res. 2005;18:427–38. PubMed PMID: 16280008.

de Sousa Andrade SM, Monteiro AR, Martins JH, Alves MC, Santos Silva LF, Quadros JM, Ribeiro CA. Cochlear implant rehabilitation outcomes in Waardenburg syndrome children. Int J Pediatr Otorhinolaryngol. 2012;76:1375–8. PubMed PMID: 22784507.

DeStefano AL, Cupples LA, Arnos KS, Asher JH, Baldwin CT, Blanton S, Carey ML, da Silva EO, Friedman TB, Greenberg J, Lalwani AK, Milunsky A, Nance WE, Pandya A, Ramesar RS, Read AP, Tassabejhi M, Wilcox ER, Farrer LA. Correlation between Waardenburg syndrome phenotype and genotype in a population of individuals with identified PAX3 mutations. Hum Genet. 1998;102:499–506. PubMed PMID: 9654197.

Elmaleh-Bergès M, Baumann C, Noel-Petroff N, Sekkal A, Couloigner V, Devriendt K, Wilson M, Marlin S, Sebag G, Pingault V. Spectrum of temporal bone abnormalities in patients with Waardenburg syndrome and SOX10 mutations. AJNR Am J Neuroradiol. 2013;34:1257–63. PubMed PMID: 23237859.

Farrer LA, Grundfast KM, Amos J, Arnos KS, Asher JH, Beighton P, Diehl SR, Fex J, Foy C, Friedman TB, et al. Waardenburg syndrome (WS) type I is caused by defects at multiple loci, one of which is near ALPP on chromosome 2: first report of the WS consortium. Am J Hum Genet. 1992;50:902–13. PubMed PMID: 1349198.

Fleming A, Copp AJ. Embryonic folate metabolism and mouse neural tube defects. Science. 1998;280:2107–9. PubMed PMID: 9641914.

Gad A, Laurino M, Maravilla KR, Matsushita M, Raskind WH. Sensorineural deafness, distinctive facial features, and abnormal cranial bones: a new variant of Waardenburg syndrome? Am J Med Genet A. 2008;146A:1880–5. PubMed PMID: 18553554.

Hoth CF, Milunsky A, Lipsky N, Sheffer R, Clarren SK, Baldwin CT. Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). Am J Hum Genet. 1993;52:455–62. PubMed PMID: 8447316.

Iso M, Fukami M, Horikawa R, Azuma N, Kawashiro N, Ogata T. SOX10 mutation in Waardenburg syndrome type II. Am J Med Genet A. 2008;146A:2162–3. PubMed PMID: 18627047.

Jan IA, Stroedter L, Haq AU, Din ZU. Association of Shah-Waardenburgh syndrome: a review of 6 cases. J Pediatr Surg. 2008;43:744–7. PubMed PMID: 18405726.

Jones KL, Smith DW, Harvey MA, Hall BD, Quan L. Older paternal age and fresh gene mutation: data on additional disorders. J Pediatr. 1975;86:84–8. PubMed PMID: 1110452.

Kapur S, Karam S. Germ-line mosaicism in Waardenburg syndrome. Clin Genet. 1991;39:194–8. PubMed PMID: 2036740.

Koyama H, Kashio A, Sakata A, Tsutsumiuchi K, Matsumoto Y, Karino S, Kakigi A, Iwasaki S, Yamasoba T. The hearing outcomes of cochlear implantation in Waardenburg syndrome. Biomed Res Int. 2016;2016:2854736. PubMed PMID: 27376080.

Kujat A, Veith VP, Faber R, Froster UG. Prenatal diagnosis and genetic counseling in a case of spina bifida in a family with Waardenburg syndrome type I. Fetal Diagn Ther. 2007;22:155–8. PubMed PMID: 17139175.

Léger S, Balguerie X, Goldenberg A, Drouin-Garraud V, Cabot A, Amstutz-Montadert I, Young P, Joly P, Bodereau V, Holder-Espinasse M, Jamieson RV, Krause A, Chen H, Baumann C, Nunes L, Dollfus H, Goossens M, Pingault V. Novel and recurrent non-truncating mutations of the MITF basic domain: genotypic and phenotypic variations in Waardenburg and Tietz syndromes. Eur J Hum Genet. 2012;20:584–7. PubMed PMID: 22258527.

Lemay P, Guyot MC, Tremblay É, Dionne-Laporte A, Spiegelman D, Henrion É, Diallo O, De Marco P, Merello E, Massicotte C, Désilets V, Michaud JL, Rouleau GA, Capra V, Kibar Z. Loss-of-function de novo mutations

play an important role in severe human neural tube defects. J Med Genet. 2015;52:493–7. PubMed PMID: 25805808.

Liu XZ, Newton VE, Read AP. Waardenburg syndrome type II: phenotypic findings and diagnostic criteria. Am J Med Genet. 1995;55:95–100. PubMed PMID: 7702105.

Madden C, Halsted MJ, Hopkin RJ, Choo DI, Benton C, Greinwald JH Jr. Temporal bone abnormalities associated with hearing loss in Waardenburg syndrome. Laryngoscope. 2003;113:2035–41. PubMed PMID: 14603070.

Matsunaga T, Mutai H, Namba K, Morita N, Masuda S. Genetic analysis of PAX3 for diagnosis of Waardenburg syndrome type I. Acta Otolaryngol. 2013;133:345–51. PubMed PMID: 23163891.

Merchant SN, McKenna MJ, Baldwin CT, Milunsky A, Nadol JB Jr. Otopathology in a case of type I Waardenburg's syndrome. Ann Otol Rhinol Laryngol. 2001;110:875–82. PubMed PMID: 11558766.

Milunsky JM, Maher TA, Ito M, Milunsky A. The value of MLPA in Waardenburg syndrome. Genet Test. 2007;11:179–82. PubMed PMID: 17627390.

Newton VE. Clinical features of the Waardenburg syndromes. Adv Otorhinolaryngol. 2002;61:201–8. PubMed PMID: 12408085.

Ohtani S, Skinkai Y, Horibe A, Katayama K, Tsuji T, Matsushima Y, Tachibana M, Kunieda T. A deletion in the endothelin-B receptor gene is responsible for the Waardenburg syndrome-like phenotypes of WS4 mice. Exp Anim. 2006;55:491–5. PubMed PMID: 17090968.

Pardono E, van Bever Y, van den Ende J, Havrenne PC, Iughetti P, Maestrelli SR, Costa F O, Richieri-Costa A, Frota-Pessoa O, Otto PA. Waardenburg syndrome: clinical differentiation between types I and II. Am J Med Genet A. 2003;117A:223–35. PubMed PMID: 12599185.

Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N. Review and update of mutations causing Waardenburg syndrome. Hum Mutat. 2010;31:391–406. PubMed PMID: 20127975.

Preus M, Linstrom C, Polomeno RC, Milot J. Waardenburg syndrome--penetrance of major signs. Am J Med Genet. 1983;15:383–8. PubMed PMID: 6881207.

Sánchez-Martín M, Pérez-Losada J, Rodríguez-García A, González-Sánchez B, Korf BR, Kuster W, Moss C, Spritz RA, Sánchez-García I. Deletion of the SLUG (SNAI2) gene results in human piebaldism. Am J Med Genet A. 2003;122A:125–32. PubMed PMID: 12955764.

Sato-Jin K, Nishimura EK, Akasaka E, Huber W, Nakano H, Miller A, Du J, Wu M, Hanada K, Sawamura D, Fisher DE, Imokawa G. Epistatic connections between micropthalmia-associated transcription factor and endothelin signaling in Waardenburg syndrome and other pigmentary disorders. FASEB J. 2008;22:1155–68. PubMed PMID: 18039926.

Shields CL, Nickerson SJ, Al-Dahmash S, Shields JA. Waardenburg syndrome: iris and choroidal hypopigmentation: findings on anterior and posterior segment imaging. JAMA Ophthalmol. 2013;131:1167–73. PubMed PMID: 23868078.

Sommer A, Bartholomew DW. Craniofacial-deafness-hand syndrome revisited. Am J Med Genet A. 2003;123A:91–4. PubMed PMID: 14556253.

Sznajer Y, Coldea C, Meire F, Delpierre I, Sekhara T, Touraine RL. A de novo SOX10 mutation causing severe type 4 Waardenburg syndrome without Hirschsprung disease. Am J Med Genet A. 2008;146A:1038–41. PubMed PMID: 18348267.

Tamayo ML, Gelvez N, Rodriguez M, Florez S, Varon C, Medina D, Bernal JE. Screening program for Waardenburg syndrome in Colombia: clinical definition and phenotypic variability. Am J Med Genet A. 2008;146A:1026–31. PubMed PMID: 18241065.

Tassabehji M, Read AP, Newton VE, Harris R, Balling R, Gruss P, Strachan T. Waardenburg's syndrome patients have mutations in the human homologue of the Pax-3 paired box gene. Nature. 1992;355:635–6. PubMed PMID: 1347148.

Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. Am J Hum Genet. 1951;3:195–253. PubMed PMID: 14902764.

Wang J, Li S, Xiao X, Wang P, Guo X, Zhang Q. PAX3 mutations and clinical characteristics in Chinese patients with Waardenburg syndrome type 1. Mol Vis. 2010;16:1146–53. PubMed PMID: 20664692.

Wang Q, Fang WH, Krupinski J, Kumar S, Slevin M, Kumar P. Pax genes in embryogenesis and oncogenesis. J Cell Mol Med. 2008;12:2281–94. PubMed PMID: 18627422.

Wildhardt G, Zirn B, Graul-Neumann LM, Wechtenbruch J, Suckfull M, Buske A, Bohring A, Kubisch C, Vogt S, Strobl-Wildemann G, Greally M, Bartsch O, Steinberger D. Spectrum of novel mutations found in Waardenburg syndrome types 1 and 2: implications for molecular genetic diagnostics. BMJ Open. 2013;3(3) doi: 10.1136/bmjopen-2012-001917. PubMed PMID: 23512835.

Wollnik B, Tukel T, Uyguner O, Ghanbari A, Kayserili H, Emiroglu M, Yuksel-Apak M. Homozygous and heterozygous inheritance of PAX3 mutations causes different types of Waardenburg syndrome. Am J Med Genet A. 2003;122A:42–5. PubMed PMID: 12949970.

Wu TF, Yao YL, Lai IL, Lai CC, Lin PL, Yang WM. Loading of PAX3 to Mitotic Chromosomes Is Mediated by Arginine Methylation and Associated with Waardenburg Syndrome. J Biol Chem. 2015;290:20556–64. PubMed PMID: 26149688.

Yang S, Dai P, Liu X, Kang D, Zhang X, Yang W, Zhou C, Yang S, Yuan H. Genetic and phenotypic heterogeneity in Chinese patients with Waardenburg syndrome type II. PLoS One. 2013;8:e77149. PubMed PMID: 24194866.

Zhang H, Chen H, Luo H, An J, Sun L, Mei L, He C, Jiang L, Jiang W, Xia K, Li JD, Feng Y. Functional analysis of Waardenburg syndrome-associated PAX3 and SOX10 mutations: report of a dominant-negative SOX10 mutation in Waardenburg syndrome type II. Hum Genet. 2012;131:491–503. PubMed PMID: 21965087.

Chapter Notes

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Revision History

- 4 May 2017 (sw) Revision: W index calculator tool added
- 12 January 2017 (sw) Comprehensive update posted live
- 7 August 2014 (me) Comprehensive update posted live
- 29 December 2011 (me) Comprehensive update posted live
- 4 August 2009 (me) Comprehensive update posted live
- 19 April 2007 (jm) Revision: deletion/duplication analysis clinically available
- 17 January 2006 (me) Comprehensive update posted live
- 22 October 2003 (me) Comprehensive update posted live
- 30 July 2001 (me) Review posted live

- 12 February 2001 (jm) Original submission

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