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Waardenburg Syndrome Type I

Jeff Mark Milunsky, MD[1]

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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 the possibly increased risk for neural tube defects associated with WS1.

Author Affiliation: 1 Director, Clinical Genetics, Senior Director, Molecular Genetics, Co-Director, Center for Human Genetics, Inc, Cambridge, Massachusetts; Email: jmilunsky@chginc.org.

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 a pregnancy 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.

Minami et al [2019] reported that 61% of individuals with WS1 (based on W index >1.95) from a Japanese cohort had pathogenic variants identified in *MITF*, *SOX10*, or *EDNRB* rather than *PAX3*, suggesting that use of a W index >1.95 is not valid for all ethnicities.

Establishing the Diagnosis

The clinical 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 (or likely pathogenic) variant in *PAX3* by molecular genetic testing (see Table 1) confirms the diagnosis if clinical features are inconclusive.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this section is understood to include any likely pathogenic variant. (2) Identification of a heterozygous *PAX3* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with hearing loss are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *PAX3* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *PAX3* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. (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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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]
Unknown	NA	<4% [7]

NA = not applicable
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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]; Wildhardt et al [2013]; Milunsky, unpublished data
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as 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.
7. One individual with a clinical diagnosis of Waardenburg syndrome type 1 (WS1) was found to have a heterozygous pathogenic variant in *MITF* [Li et al 2020]; another individual with WS1 was found to have biallelic *EDNRB* pathogenic variants [Morimoto et al 2018].

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. Waardenburg Syndrome Type I: Frequency of Select Features

Feature	% of Persons w/Feature
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 sensorineural. The most common type of hearing loss 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) have 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. This finding 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 PAX3* pathogenic nonsense 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 Waardenburg syndrome type III [Hoth et al 1993], and the p.Asn47Lys pathogenic variant, which is 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 (WS1 and Waardenburg syndrome type II [WS2] combined phenotype).** Yang et al [2013] reported a family in which one parent had WS1 as the result of a heterozygous pathogenic variant in *PAX3* and the other parent had WS2 (see Differential Diagnosis) as the result of 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

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

Other phenotypes associated with germline pathogenic variants in *PAX3* are summarized in Table 3.

Table 3. *PAX3* Allelic Disorders

Disorder	Clinical Characteristics / Comment
Waardenburg syndrome type III (WS3) (OMIM 148820)	Characterized by combination of typical WS1 features & hypoplasia or contractures of limb muscles or joints, carpal bone fusion, or syndactyly [1]
Craniofacial-deafness-hand syndrome (CDHS) (OMIM 122880)	Heterozygous *PAX3* pathogenic variants have been identified in persons w/CDHS. CDHS is characterized by flat facial profile, widely spaced eyes, hypoplastic nose w/ slit-like nares, sensorineural hearing loss, small maxilla, absent or small nasal bones, & ulnar deviation of hands. The author suggests that CDHS may be genetically heterogeneous.

WS1 = Waardenburg syndrome type 1

1. 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 *PAX3* p.Tyr90His pathogenic variant, has WS3 [Wollnik et al 2003].

Differential Diagnosis

Waardenburg syndrome type I (WS1) needs to be differentiated from other causes of congenital, non-progressive sensorineural hearing loss (see Hereditary Hearing Loss and Deafness 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 4).

Table 4. Comparison of Clinical Features in Waardenburg Syndrome Type I and Waardenburg Syndrome Type II

Clinical Finding	% of Affected Persons	
	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%

Table 4. continued from previous page.

Clinical Finding	% of Affected Persons	
	WS1	WS2
Early graying	23%-38%	14%-30%
Leukoderma	22%-36%	5%-12%
High nasal root	52%-100%	0%-14%
Medial eyebrow flare	63%-73%	7%-12%

Based on Liu et al [1995], Pardono et al [2003], Tamayo et al [2008]
WS1 = Waardenburg syndrome type I; WS2 = Waardenburg syndrome type II

Table 5. Genes of Interest in the Differential Diagnosis of Waardenburg Syndrome Type I

Gene(s)	Disorder	MOI	Clinical Features / Comment
KITLG *MITF* *SNAI2* *SOX10*	WS2 (OMIM PS193500)	AD AR	*MITF* pathogenic variants account for ~10%-20% of WS2. *SNAI2* pathogenic variants were reported in 2 persons w/features overlapping w/WS2. *SOX10* pathogenic variants account for ~15% of WS2. (Temporal bone abnormalities [1] are reported in persons w/*SOX10* pathogenic variants. [2])
EDN3 *EDNRB* *SOX10*	WS4 (OMIM PS193500)	AD AR	Pigmentary abnormalities, hearing loss, & Hirschsprung disease [3]
KIT *SNAI2*	Piebaldism (OMIM 172800)	AD	Piebaldism has some pigmentary features in common w/WS. A white forelock is common, as well as absent pigmentation of medial forehead & eyebrows. Absent pigmentation of chest, abdomen, & limbs is also common. Presence of hyperpigmented borders surrounding unpigmented areas is characteristic. Heterochromic irides & sensorineural deafness are rarely described.
MITF	Tietz syndrome (OMIM 103500)	AD	Albinism & deafness

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; WS = Waardenburg syndrome; WS2 = Waardenburg syndrome type II; WS4 = Waardenburg syndrome type IV
1. Bilateral agenesis or hypoplasia of the semicircular canals with a cochlear deformity and enlarged vestibule
2. Elmaleh-Bergès et al [2013]
3. Jan et al [2008]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Waardenburg syndrome type I (WS1), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Audiology evaluation
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of WS1 in order to facilitate medical and personal decision making

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 Waardenburg syndrome [Amirsalari et al 2012, de Sousa Andrade et al 2012, Koyama et al 2016, Fan et al 2022].

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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise 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.
- Recommendations for the evaluation of parents of a proband who appears to be the only affected family member (i.e., a simplex case) can include the following:
  - Examination for clinical manifestations of WS1 by assessing facial features, calculating the W index, examining skin and hair for hypopigmentation, and obtaining an audiogram
  - If a molecular diagnosis has been established in the proband, molecular genetic testing to confirm the genetic status of the parents and to allow reliable recurrence risk counseling

- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Kapur & Karam 1991, Chen et al 2018]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with WS1 may appear to be negative because of a milder phenotypic presentation in a parent. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents.

- If a parent of the proband is affected and/or is known to have the *PAX3* pathogenic variant identified in the proband, the risk to the sibs is 50%.

  Intrafamilial clinical variability is observed in WS1. The clinical manifestations in a sib who inherits a *PAX3* pathogenic variant cannot be predicted by the phenotype in other affected family members and can range from mild or subclinical features through the classic phenotype of WS1, including deafness.

- If the proband has a known *PAX3* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Kapur & Karam 1991, Chen et al 2018].

- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of parental germline mosaicism [Kapur & Karam 1991, Chen et al 2018].

Offspring of a proband

- Each child of an individual with WS1 has a 50% chance of inheriting the *PAX3* pathogenic variant.
- The clinical manifestations in the offspring who inherit a *PAX3* pathogenic variant cannot be predicted and can 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 and/or is known to have the *PAX3* pathogenic variant, the parent's family members may be 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.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *PAX3* pathogenic variant has been identified in an affected family member, prenatal 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. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **MedlinePlus**
  Waardenburg syndrome
- **NCBI Genes and Disease**
  Waardenburg syndrome
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  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.
  babyhearing.org
- **Hereditary Hearing Loss Homepage**
  www.hereditaryhearingloss.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **National Organization for Albinism and Hypopigmentation (NOAH)**
  Phone: 800-473-2310 (US and Canada); 603-887-2310
  Fax: 603-887-6049

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
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 paired box protein Pax-3 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 Pax-3 to bind to and regulate reporter genes fused to either the *MITF* or *TYRP1* (encoding tyrosinase-related protein 1) promoters [Corry & Underhill 2005]. Hence, Pax-3 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 Pax-3 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 Pax-3 homeodomain, whereas others affect its interaction with DNA. Wu et al [2015] have examined the loading of *PAX3* on mitotic chromosomes in zebra fish and suggest that mutated Pax-3 proteins have dominant-negative effects.

Mechanism of disease causation. Loss of function (haploinsufficiency)

Table 6. Notable *PAX3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_181457.4 NP_852122.1	c.139A>C	p.Asn47His	See Genotype-Phenotype Correlations.
	c.141C>G	p.Asn47Lys	
	c.268T>C	p.Tyr90His	See Genetically Related Disorders.

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Somatic *PAX3* variants have been observed in alveolar rhabdomyosarcoma. *PAX3* can fuse with *FKHR*, 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.

Chapter Notes

Author Notes

Dr Milunsky was previously a Professor in the Department of Pediatrics, Genetics, and Genomics at Boston University School of Medicine. He is currently the Co-Director of the Center for Human Genetics, Inc (Cambridge, MA), where he also serves as Senior Molecular Director and Director of Clinical Genetics. His interest in Waardenburg syndrome predates the identification of *PAX3*, when he was involved in gene mapping of several families with WS1.

Revision History

- 20 October 2022 (sw) Comprehensive update posted live
- 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

References

Published Guidelines / Consensus Statements

- American College of Medical Genetics. Statement on universal newborn hearing screening. Available online. 2000. Accessed 10-11-22.
- 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 10-24-22.

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.

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.

Chen K, Zhan Y, Wu X, Zong L, Jiang H. Germinal mosaicism of PAX3 mutation caused Waardenburg syndrome type I. Int J Pediatr Otorhinolaryngol. 2018;104:200–4. PubMed PMID: 29287868.

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.

Fan W, Ni K, Chen F, Li X. Hearing characteristics and cochlear implant effects in children with Waardenburg syndrome: a case series. Transl Pediatr. 2022;11:1234–41. PubMed PMID: 35958009.

Farrer LA, Grundfast KM, Amos J, Arnos KS, Asher JH, Beighton P, Diehl SR, Fex J, Foy C, Friedman TB, Greenberg J, Hoth C, Marazita M, Milunsky A, Morell R, Nance W, Newton V, Ramesar R, San Agustin TB, Skare J, Stevens CA, Wagner RG, Wilcox ER, Winship I, Read AP. 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.

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.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

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.

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.

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.

Li W, Feng Y, Chen H, He C, Mei L, Liu XZ, Men M. MITF Is Mutated in Type 1 Waardenburg Syndrome with Unusual Phenotype. Otol Neurotol. 2020;41:e1250–5. PubMed PMID: 32740552.

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.

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.

Minami SB, Nara K, Mutai H, Morimoto N, Sakamoto H, Takiguchi T, Kaga K, Matsunaga T. A clinical and genetic study of 16 Japanese families with Waardenburg syndrome. Gene. 2019;704:86–90. PubMed PMID: 30978479.

Morimoto N, Mutai H, Namba K, Kaneko H, Kosaki R, Matsunaga T. Homozygous EDNRB mutation in a patient with Waardenburg syndrome type 1. Auris Nasus Larynx. 2018;45:222–6. PubMed PMID: 28502583.

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

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.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

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.

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.

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:e001917.

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.

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