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# *PAX6*-Related Aniridia

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## Summary

### Clinical characteristics

*PAX6*-related aniridia occurs either as an isolated ocular abnormality or as part of the *W*ilms tumor-*a*niridia-*g*enital anomalies-*r*etardation (WAGR) syndrome. Aniridia is a pan ocular disorder affecting the cornea, iris, intraocular pressure (resulting in glaucoma), lens (cataract and lens subluxation), fovea (foveal hypoplasia), and optic nerve (optic nerve coloboma and hypoplasia). Individuals with aniridia characteristically show nystagmus and impaired visual acuity (usually 20/100 - 20/200); however, milder forms of aniridia with subtle iris architecture changes, good vision, and normal foveal structure do occur. Other ocular involvement may include strabismus and occasionally microphthalmia. Although the severity of aniridia can vary between and within families, little variability is usually observed in the two eyes of an affected individual.

*WAGR syndrome.* The risk for Wilms tumor is 42.5%-77%; of those who develop Wilms tumor, 90% do so by age four years and 98% by age seven years. Genital anomalies in males can include cryptorchidism and hypospadias (sometimes resulting in ambiguous genitalia), urethral strictures, ureteric abnormalities, and gonadoblastoma. While females typically have normal external genitalia, they may have uterine abnormalities and streak ovaries. Intellectual disability (defined as IQ <74) is observed in 70%; behavioral abnormalities include attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, anxiety, depression, and obsessive-compulsive disorder. Other individuals with WAGR syndrome can have normal intellect without behavioral issues.

### Diagnosis/testing

The diagnosis of *PAX6*-related aniridia is established in a proband with one of the two following clinical and molecular genetic findings:

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- Isolated aniridia (i.e., without systemic involvement) and a heterozygous *PAX6* pathogenic variant, ranging in size from a single nucleotide (e.g., those resulting in a nonsense, missense, or splice site variant or single-nucleotide deletion or duplication) to a partial- or whole-gene deletion (or in rare instances deletions telomeric to *PAX6* that do not include *PAX6*); or
- Aniridia and one or more additional findings of WAGR syndrome and a deletion of *PAX6* and the upstream adjacent gene, *WT1*

## Management

*Treatment of manifestations:*

- *Aniridia.* Correction of refractive errors, use of tinted or photochromic lenses to reduce light sensitivity, occlusion therapy in childhood for amblyopia, use of low-vision aids. Treatment of severe cataracts requires attention to potential complications caused by poor zonular stability. Glaucoma: Initial treatment is usually topical anti-glaucoma medication; surgery is reserved for eyes that do not respond to medical therapy. Ocular surface disease: medical treatment (lubricants, mucolytics, and punctal occlusion) may help slow the progression of corneal opacification. When corneal opacification causes significant visual reduction, penetrating keratoplasty with limbal stem cell transplantation may be considered; however, this has a high risk of failure and possible lifelong systemic immunosuppression to prevent rejection.
- *WAGR syndrome*. Wilms tumor, genital anomalies, and developmental delay / intellectual disability are managed as per standard practice.

*Surveillance:*

- *Aniridia.* Monitor children younger than age eight years every four to six months for refractive errors and detection and treatment of incipient or actual amblyopia; annual ophthalmology follow up of all individuals to detect issues such as corneal changes, raised intraocular pressure, and cataracts.
- *WAGR syndrome*. Children with aniridia and a *WT1* deletion require renal ultrasound examinations every three months and follow up by a pediatric oncologist until age eight years. Because of the increased risk for renal impairment in WAGR syndrome (especially in those with bilateral Wilms tumor), lifelong evaluation of renal function is recommended. Developmental progress and educational needs require regular monitoring. Behavioral assessment for anxiety, ADHD, and aggressive or self-injurious behavior as needed.

*Agents/circumstances to avoid:* Intraocular surgery may increase the likelihood of (or exacerbate existing) keratopathy; repeated intraocular surgery predisposes to severe aniridic fibrosis syndrome.

*Evaluation of relatives at risk:* Early clarification of the genetic status of infants who are offspring or sibs of an individual with *PAX6*-related isolated aniridia (by either an eye examination or molecular genetic testing for the *PAX6* variant in the family) is recommended in order to identify those who would benefit from prompt treatment and surveillance of complications of aniridia.

## Genetic counseling

Isolated aniridia and WAGR syndrome are inherited in an autosomal dominant manner.

- *Isolated aniridia.* ~70% of individuals have an affected parent; ~30% have a *de novo PAX6* pathogenic variant or deletion of a regulatory region controlling *PAX6* expression. Each child of an individual with isolated aniridia has a 50% chance of inheriting the causative genetic alteration and developing aniridia. In rare instances of mosaicism for the *PAX6* pathogenic variant in the proband, the risk to offspring may be lower.

- *WAGR syndrome* is associated with contiguous-gene deletions including *PAX6* and *WT1*. If the proband has a *de novo* contiguous-gene deletion and neither parent has evidence of mosaicism for the deletion, the risk to sibs is no greater than that in the general population.

When the *PAX6* genetic alteration in a family is known, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

## *GeneReview* Scope

| *PAX6*-Related Aniridia: Included Phenotypes |
| --- |
| • Isolated aniridia<br>• *W*ilms *t*umor-*a*niridia-*g*enital anomalies-*r*etardation (WAGR) syndrome |

## Diagnosis

*PAX6*-related aniridia includes isolated aniridia without systemic involvement and the *W*ilms tumor-*a*niridia-*g*enital anomalies-*r*etardation (WAGR) syndrome. No formal diagnostic criteria have been published.

### Suggestive Findings

***PAX6*-related isolated aniridia** should be suspected in probands who have the following clinical and imaging findings of aniridia with no other associated systemic abnormalities.

**Clinical findings**

- Aniridia. Complete or partial iris hypoplasia best seen on slit lamp examination. Iris translucency or abnormal architecture and pupillary abnormalities may also be seen.
- Reduced visual acuity secondary to:
  - Absence of or reduction in the normal foveal architecture (usually [not always] observed)
  - Optic nerve abnormalities (e.g., optic nerve hypoplasia or coloboma)
- Early-onset nystagmus (usually apparent by age 6 weeks)
- Microphthalmia and ocular coloboma (iris, chorioretinal, and/or optic disc)

**Imaging findings**

- **Optical coherence tomography (OCT)** may be used to document foveal hypoplasia. Although OCT is difficult to perform in the presence of nystagmus, useful images can be obtained with persistence. This should be routinely performed to support a clinical diagnosis, especially where iris defects may be subtle. Anterior segment OCT can also be used to delineate the detailed anatomy of the anterior segment structures, even in those with corneal opacity [Majander et al 2012].
- **Ultrasound B-scan** should be performed routinely to assess axial length due to the association with microphthalmia.
- **High-frequency ultrasound biomicroscopy.** In infants with corneal opacity or severe corneal edema resulting from associated congenital glaucoma, high-frequency anterior segment ultrasound examination, usually performed under anesthesia, can demonstrate iris hypoplasia and/or absence [Nischal 2007].

  Note: Iris fluorescein angiography may identify subtle iris hypoplasia but is rarely used clinically.

**Wilms tumor-aniridia-genital anomalies-retardation (WAGR) syndrome** should be suspected in probands with aniridia and no family history of aniridia who also have at least one of the following findings:

- Wilms tumor (also known as nephroblastoma), a childhood kidney malignancy. Of children with WAGR who develop Wilms tumor, 90% do so by age four years and 98% by age seven years (see Wilms Tumor Predisposition).
- Genitourinary abnormalities. In males: cryptorchidism, hypospadias, ambiguous genitalia; in females: normal external female genitalia, but uterine abnormalities (heart-shaped bicornate uterus) and streak ovaries. In males and females: end-stage kidney disease, ureteric abnormalities, and gonadoblastoma.
- Intellectual disability and/or behavior abnormalities including depression, anxiety, ADHD, obsessive-compulsive disorder, and autism.
- Childhood-onset obesity and pancreatitis

## Establishing the Diagnosis

The diagnosis of *PAX6*-related aniridia is established in a proband with one of the two following clinical and molecular genetic findings (Table 1):

- **Isolated aniridia** (i.e., without systemic involvement) and a heterozygous *PAX6* pathogenic variant, ranging in size from a single nucleotide (e.g., those resulting in a nonsense, missense, or splice site variant or single-nucleotide deletion or duplication) to a partial or whole-gene deletion [Richardson et al 2016]

  Note: Deletions telomeric to *PAX6* that do not include *PAX6* have been reported.

  - A heterozygous variant in the ultraconserved *PAX6 cis*-regulatory element (SIMO) that resides 150 kb downstream from *PAX6* in intron 9 of *ELP4* (NM_001288726.1) causes isolated aniridia [Bhatia et al 2013].
  - MLPA detected a 0.6-Mb deletion downstream of *PAX6* on chromosome 11 that encompasses *DCDC1*, *DPH4*, *IMMP1L*, and *ELP4* [Wawrocka et al 2012].

  Coverage of these regions on chromosomal or gene-targeted arrays will vary [Blanco-Kelly et al 2017, Franzoni et al 2017].

- **Wilms tumor-aniridia-*g*enital anomalies-*r*etardation (WAGR) syndrome** and EITHER of the following:

  - A deletion of *PAX6* and the upstream adjacent gene, *WT1*

    Note: Reported deletions include the recurrent 11p13 deletion (see Table 1).

  - One or more additional findings of WAGR syndrome found on physical examination in individuals with aniridia.

    Note: If the child has not had genetic testing, the clinical diagnosis of WAGR syndrome usually cannot be established or ruled out until a child has passed through the age of risk for Wilms tumor, intellectual disability, and behavior abnormalities.

Molecular genetic testing can establish the molecular basis of aniridia, and thus distinguish between isolated aniridia (no increased risk for Wilms tumor) and WAGR (markedly increased risk for Wilms tumor). In the following scenarios molecular genetic testing approaches are based on the individual's age, clinical findings, family history, and testing methods available.

### Scenario 1

**The proband is an infant with aniridia who represents a simplex case (i.e., a single occurrence in the family).**

**Option 1**

1. Perform chromosomal microarray (CMA) (which may use array-based comparative genomic hybridization [aCGH] and/or a SNP genotyping array) to identify a contiguous-gene deletion that includes *PAX6* and *WT1*.

   **Note:** (1) Although routine (genomic) CMA will detect an 11p13 WAGR deletion, other gene-targeted CMA designs may be used to identify either a *PAX6-WT1* contiguous-gene deletion OR whole-gene or partial deletion of *PAX6*. (2) Deletions telomeric to *PAX6* that do not include *PAX6* have been reported [Wawrocka et al 2012, Blanco-Kelly et al 2017, Franzoni et al 2017]. Coverage of these regions (e.g., intron 9 of *ELP4*) on chromosomal or gene-targeted arrays will vary.

2. If a deletion involving *PAX6* and *WT1* is not identified, perform sequence analysis of *PAX6*.

   **Note:** Genome sequencing (GS) is likely to enable screening of intronic regions (e.g., the SIMO of *ELP4*) or chromosomal rearrangements (e.g., deletions in *ELP4*); however, individual genomic regions will need to be examined for coverage and quality of sequence. GS is not yet part of routine care in most centers.

**Option 2**

1. Perform sequence analysis of *PAX6*.

   **Note:** The first three exons of *PAX6* are noncoding. Variants in these noncoding exons have been associated with disease [Glaser et al 1992, Grønskov et al 1999].

2. If a *PAX6* pathogenic variant is not identified, perform CMA to identify a contiguous-gene deletion that includes *PAX6* and *WT1*.

   **Note:** Although routine CMA will detect an 11p13 WAGR deletion, other gene-targeted CMA designs may be used to identify either a *PAX6-WT1* contiguous-gene deletion OR whole-gene or partial deletion of *PAX6*.

## Scenario 2

**The proband is thought to have isolated aniridia because (a) there is a positive family history of isolated aniridia or (b) the proband has exceeded the age of risk for Wilms tumor.**

1. Perform *PAX6* sequence analysis.

   **Note:** The first three exons of *PAX6* are noncoding. Variants in these noncoding exons have been associated with disease [Glaser et al 1994, Grønskov et al 1999].

2. If no *PAX6* pathogenic variant is identified, perform CMA to investigate for any contiguous-gene deletions/duplications involving *PAX6* or *WT1*; or consider sequence analysis and/or deletion/duplication analysis to also include the SIMO region of *ELP4*.

## Scenario 3

**The proband is either an infant with aniridia and genital anomalies or an older individual with aniridia and intellectual disability and/or Wilms tumor and/or genital anomalies.** Perform CMA to identify a contiguous-gene deletion that includes *PAX6* and *WT1*.

**Table 1.** Molecular Genetic Testing Used in *PAX6*-Related Aniridia

| Disorder | Proportion of Probands | Genes [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method &Phenotype |
|---|---|---|---|---|
| Isolated aniridia | 2/3 [3] | *PAX6* | Sequence analysis [4] | ~85% [5, 6] |
| | | | Gene-targeted deletion/ duplication analysis [7] | ~15% [8] |
| WAGR [9]: ~700-kb heterozygous deletion at 11p13 [10] ISCA-37401 [11] | 1/3 [3] | *PAX6* & *WT1* | CMA [12] | 100% |
| | | | FISH [13, 14] | 100% |

*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.* Grønskov et al [2001], Robinson et al [2008], Blanco-Kelly et al [2017], Vasilyeva et al [2017]
*4.* 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, C-terminal extension (CTE) variants 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.
*5.* Redeker et al [2008], Bobilev et al [2016], Richardson et al [2016], Blanco-Kelly et al [2017], Sannan et al [2017], Vasilyeva et al [2017]
*6.* In one individual a heterozygous single-nucleotide variant in the ultraconserved *PAX6 cis*-regulatory element (SIMO) (residing 150 kb downstream from *PAX6* in intron 9 of *ELP4*) has been reported to cause isolated aniridia [Bhatia et al 2013].
*7.* 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.
*8.* Leiden Open Variation Database (LOVD) and Chao et al [2003], Redeker et al [2008], Aradhya et al [2012], Lim et al [2012], Han et al [2013], Ansari et al [2016], Bobilev et al [2016], Blanco-Kelly et al [2017], Vasilyeva et al [2017]. Note: Many reported large deletions (encompassing *PAX6* but not *WT1* OR involving *EPL4* and *DCDC1* downstream of *PAX6*) would be detectable by CMA.
*9.* Wilms tumor-aniridia-genital anomalies-retardation (WAGR) syndrome caused by deletion of *PAX6* and *WT1*
*10.* GRCh37/hg19 chr11:31,803,509-32,510,988: Genomic coordinates represent the minimum deletion size associated with the 11p13 recurrent deletion as designated by ClinGen. Deletion coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the deletion as calculated from these genomic positions may differ from the expected deletion size due to the presence of segmental duplications near breakpoints.
*11.* Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium)
*12.* Chromosome microarray analysis (CMA) using oligonucleotide arrays (i.e., array comparative genomic hybridization) and/or SNP genotyping arrays. CMA designs in current clinical use target the 11p13 region.
*13.* FISH is not appropriate as a diagnostic method for an individual in whom the 11p13 deletion syndrome was not detected by CMA designed to target this region.
*14.* FISH, qPCR, or other quantitative methods of targeted deletion analysis can be used to identify the 11p13 deletion in at-risk relatives of the proband to help determine recurrence risk (see Genetic Counseling).

# Clinical Characteristics

## Clinical Description

*PAX6*-related aniridia occurs either as an isolated ocular abnormality or as part of the Wilms tumor-aniridia-genital anomalies-retardation (WAGR) syndrome. Aniridia, a congenital eye anomaly, is usually detected at birth if fully penetrant. It is often the presenting feature of WAGR; children with WAGR are at significant risk of developing Wilms tumor during early childhood.

## Aniridia

Aniridia is a pan ocular disorder affecting the cornea, iris, intraocular pressure, lens, fovea, and optic nerve. The phenotype is variable between and within families; however, affected individuals usually show little variability between the two eyes. Individuals with aniridia characteristically show nystagmus, impaired visual acuity (usually 20/100 - 20/200), and foveal hypoplasia. Milder forms of aniridia with subtle iris architecture changes, good vision, and normal foveal structure do occur [Hingorani et al 2009]. Other abnormalities include corneal changes, glaucoma, cataract, lens subluxation, strabismus, optic nerve coloboma and hypoplasia, and occasionally microphthalmia.

The reduction in visual acuity is primarily caused by foveal hypoplasia, but cataracts, glaucoma, and corneal opacification are responsible for progressive visual failure. Most children with aniridia present at birth with an obvious iris or pupillary abnormality or in infancy with nystagmus (usually apparent by age 6 weeks). Congenital glaucoma rarely occurs in aniridia; in such cases, a large corneal diameter and corneal edema may be the presenting findings. Despite their many ocular issues, most individuals with aniridia can retain useful vision with appropriate ophthalmologic management.

**Iris.** The most obvious ocular abnormality is iris hypoplasia. The severity varies from a nearly normal iris to almost complete iris absence, in which a small stump of residual iris tissue is visible on gonioscopy, anterior segment optical coherence tomography (OCT), or ultrasound biomicroscopy [Okamoto et al 2004]. In less extreme cases, the pupil size may be normal, but there may be loss of the iris surface architecture or the presence of iris transillumination [Hingorani et al 2009]. Other iris changes include partial iris defects (resembling a coloboma) or eccentric or misshapen pupils and iris ectropion [Nelson et al 1984, Willcock et al 2006].

**Lens.** Congenital lens opacities (especially polar) are common [Gramer et al 2012]. Often there is persistent vascularization of the anterior lens capsule (tunica vasculosa lentis) or remnants of the pupillary membrane. The lens opacities are rarely dense enough to require lens extraction in infancy, but visually significant lens opacities eventually develop in 50%-85% of affected individuals, often in the teens or early adulthood. Lens subluxation or dislocation occurs but is uncommon.

**Intraocular pressure.** When elevated intraocular pressure is associated with loss of retinal ganglion cells resulting in visual field loss and optic nerve cupping, a diagnosis of glaucoma is made. Both elevated intraocular pressure and glaucoma are common in people with aniridia and may eventually occur in up to two thirds of individuals [Gramer et al 2012]. The onset of glaucoma is usually in later childhood or adulthood; glaucoma in infancy is rare [Gramer et al 2012].

**Cornea.** Keratopathy (corneal degeneration) is a relatively late manifestation with multifactorial causes including limbal stem cell abnormalities and abnormal wound healing [Ramaesh et al 2005]. Changes vary from mild peripheral vascularization to pan corneal vascularization, opacification, and keratinization. Inadequate tear production is common and exacerbates the ocular surface problems. Central corneal thickness is increased – a finding of uncertain clinical relevance, but which may result in undermeasurement of intraocular pressure on tonometry [Brandt et al 2004, Whitson et al 2005]. Rarely, those with aniridia may have microcornea and, extremely rarely, megalocornea [Lipsky & Salim 2011, Wang et al 2012].

**Fovea.** Foveal hypoplasia is usually (but not always) present. Findings include reduced foveal reflex, macular hypopigmentation, and crossing of the usual foveal avascular zone by retinal vessels. OCT images can clearly delineate the absence of normal foveal architecture.

**Optic nerve.** Optic nerve hypoplasia (i.e., the optic nerve head appears abnormally small) may occur in up to 10% and there may be optic nerve colobomata [McCulley et al 2005].

**Aniridic fibrosis syndrome.** Individuals with aniridia who have a history of multiple ocular procedures (penetrating keratoplasty, intraocular lenses [IOLs], and drainage tube insertion) may rarely develop aniridic

fibrosis syndrome in which a fibrotic retrolenticular and retrocorneal membrane arises from the root of the rudimentary iris tissue. This membrane may cause forward displacement of the IOLs, IOL entrapment, and corneal decompensation [Tsai et al 2005].

**Retina.** Retinal detachment may occur, probably as a consequence of a high myopia or previous intraocular surgery. Very rarely, primary retinal manifestations such as an exudative vascular retinopathy or chorioretinal degeneration may be seen [Hingorani et al 2009, Aggarwal et al 2011].

**Other ocular manifestations.** Affected individuals may have significant refractive errors and may develop a secondary strabismus (squint, eye misalignment). Some affected individuals have microphthalmia (manifest as decreased axial length on USS B-scan) and ocular coloboma (iris, chorioretinal, and/or optic disc).

**Central nervous system.** Individuals with isolated aniridia may show reduced olfaction and cognition, behavioral issues, or developmental delay. Central nervous system abnormalities (including absence or hypoplasia of the anterior commissure; abnormalities of gray matter in the anterior cingulate cortex, cerebellum, and temporal and occipital lobes; white matter deficits in and reduced volume of the corpus callosum; absence of the pineal gland; and occasionally olfactory bulb hypoplasia) can be demonstrated on MRI [Sisodiya et al 2001, Free et al 2003, Mitchell et al 2003, Ellison-Wright et al 2004, Valenzuela & Cline 2004, Bamiou et al 2007, Abouzeid et al 2009, Grant et al 2017].

**Hearing.** Central auditory processing difficulties (from abnormal interhemispheric transfer) present in some individuals may cause hearing difficulties. This finding is particularly important in the context of associated visual impairment [Bamiou et al 2007].

## Wilms Tumor-Aniridia-Genital Anomalies-Retardation (WAGR) Syndrome

Individuals with molecularly confirmed deletions of 11p13 involving *PAX6* and *WT1* are diagnosed with WAGR syndrome [Clericuzio et al 2011, Blanco-Kelly et al 2017].

**Aniridia** is almost universally present in individuals with such a deletion and typically is complete. However, WAGR without aniridia has been described.

**Wilms tumor** risk for children with a molecularly confirmed heterozygous contiguous-gene deletion of *PAX6* and *WT1* at chromosome 11p13 is between 42.5% and 77% [Fischbach et al 2005, Clericuzio et al 2011]. Of those who develop Wilms tumor, 90% do so by age four years and 98% by age seven years. Compared to children with isolated Wilms tumor, children with WAGR syndrome are more likely to develop bilateral tumors and to have an earlier age of diagnosis and more favorable tumor histology with a better prognosis [Halim et al 2012].

Wilms tumor, also known as a nephroblastoma, is a childhood kidney malignancy. Associated features include abdominal pain, fever, anemia, hematuria, and hypertension in up to 30% of affected children. See Wilms Tumor Predisposition.

The risk of later end-stage kidney disease (ESKD) is significant, relating to Wilms tumor and its surgery, focal segmental glomerulosclerosis, and occasionally renal malformation. The rate of ESKD is 36% with unilateral Wilms tumor and 90% with bilateral Wilms tumor. Approximately 25% of individuals with WAGR syndrome have proteinuria ranging from minimal to overt nephritic syndrome [Breslow et al 2005, Fischbach et al 2005].

**Genitourinary abnormalities** include ambiguous genitalia, urethral strictures, ureteric abnormalities, and gonadoblastoma. Males display cryptorchidism (most common feature, seen in 60%) and hypospadias. Females may have uterine abnormalities including bicornate uterus and streak ovaries; their external genitalia are usually normal [Fischbach et al 2005].

**Intellectual disability and behavioral abnormalities** in WAGR syndrome are highly variable:

- Intellectual disability (defined as IQ <74) is seen in 70% of individuals with WAGR syndrome; other individuals with WAGR syndrome can have normal intellect without behavioral issues.
- Behavioral abnormalities include attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety, depression, and obsessive-compulsive disorder.

**Neurologic abnormalities** occur in up to one third of individuals with WAGR syndrome. Findings include hypertonia or hypotonia, epilepsy, enlarged ventricles, corpus callosum agenesis, and microcephaly.

**Obesity.** The association of obesity in the WAGR spectrum, for which the acronym WAGRO has been suggested, has been confirmed [Brémond-Gignac et al 2005a].

**Other.** Affected individuals may also show craniofacial dysmorphism, hemihypertrophy, growth retardation, scoliosis, and kyphosis. Other anomalies reported on occasion include polydactyly and congenital diaphragmatic hernia [Nelson et al 1984, Brémond-Gignac et al 2005b, Manoukian et al 2005, Scott et al 2005] (see Congenital Diaphragmatic Hernia Overview).

## Genotype-Phenotype Correlations

**Isolated aniridia.** *PAX6* haploinsufficiency produces classic and severe aniridia with a high incidence of sight-reducing pathology including optic nerve malformations, glaucoma, cataract, and corneal changes [Kleinjan & van Heyningen 1998, Prosser & van Heyningen 1998, Grønskov et al 1999, Hanson et al 1999, Lauderdale et al 2000, van Heyningen & Williamson 2002, Chao et al 2003, Tzoulaki et al 2005, Dansault et al 2007, Hingorani et al 2009].

*PAX6* pathogenic missense variants, particularly those that are in the paired domain and therefore likely to significantly reduce the DNA binding ability, tend to produce atypical/milder or variable-phenotype aniridia with better vision, more residual iris tissue, and a lower frequency of sight-reducing malformations and complications [Hingorani et al 2009].

C-terminal extension (CTE) pathogenic variants, which generate a longer protein product, are associated with a moderately severe aniridic phenotype with poor vision, keratopathy, and cataracts; however, individuals with CTE pathogenic variants are less likely to have glaucoma and are more likely to have preservation of iris tissue than individuals who have pathogenic null variants [Hingorani et al 2009, Aggarwal et al 2011]. For reasons that are not clear, the rare reports of significant non-foveal retinal abnormalities (exudative retinopathy, chorioretinal degeneration) are all associated with CTE pathogenic variants [Hingorani et al 2009, Aggarwal et al 2011].

## Penetrance

Isolated aniridia has almost complete penetrance.

Aniridia in WAGR also has almost complete penetrance. The risk of Wilms tumor is up to 77%.

## Prevalence

The prevalence of aniridia is 1:40,000 to 1:100,000. No racial or sexual differences are recognized.

The prevalence of WAGR syndrome is approximately 1:500,000.

# Genetically Related (Allelic) Disorders

***PAX6* heterozygous pathogenic variants.** Heterozygous pathogenic missense variants with residual protein function produce alternative ocular and sometimes neurodevelopmental phenotypes (detailed in Table 2) [Prosser & van Heyningen 1998, Hanson et al 1999, Azuma et al 2003, Vincent et al 2003, Dansault et al 2007]. All are inherited in an autosomal dominant manner.

**Table 2.** Other Autosomal Dominant Ocular Phenotypes Caused by *PAX6* Pathogenic Variants

| Ocular Phenotype | Manifestations |
|---|---|
| Keratitis | Limbal stem cell deficiency w/vascularization & opacification of the cornea ± foveal hypoplasia |
| Microcornea | Small corneas w/diameters <10 mm |
| Peters anomaly [1] | Central corneal opacity caused by iridocorneal adhesions or lenticulocorneal adhesions; glaucoma in 50% |
| Ectopia pupillae | Pupil displaced from center of iris |
| Juvenile cataracts | Early-onset lens opacities |
| Isolated foveal hypoplasia | Normal iris, reduced foveal reflex, reduced macular pigmentation, retinal vessels crossing the usually avascular foveal zone |
| Optic nerve aplasia/hypoplasia or coloboma | Small, absent, or malformed optic nerve heads |
| Microphthalmia, cataract, & nystagmus | Very small eye, early lens opacities; glaucoma common |
| Foveal hypoplasia/macular coloboma w/ neurodevelopmental anomalies | Absent or highly malformed central chorioretinal area, variable neurologic abnormalities (e.g., cerebellar syndrome, cortical atrophy, low IQ, absent pineal gland) |
| Nystagmus, foveal hypoplasia, & presenile cataract [2] | |

From webapps.igc.ed.ac.uk/world/lsdb
*1.* *PAX6* pathogenic variants have not been detected in most individuals with Peters anomaly [Churchill et al 1998, Chavarria-Soley et al 2006, Dansault et al 2007].
*2.* Thomas et al [2014]; Author, personal observation

**Biallelic *PAX6* pathogenic loss-of-function variants.** In the rare cases of a homozygous or compound heterozygous *PAX6* variant, severe craniofacial abnormalities, anophthalmia, absent or malformed nose, absent adrenal glands, central nervous system malformations, and often fetal or neonatal death have occurred [Hodgson & Saunders 1980, Glaser et al 1994, Schmidt-Sidor et al 2009].

# Differential Diagnosis

## Individuals with Aniridia and No Identifiable *PAX6* Pathogenic Variant

Heterozygous pathogenic variants in the following genes are included in the differential diagnosis of *PAX6*-related aniridia:

- ***FOXC1.*** Phenocopies exist and include dominant alleles of *FOXC1*, which can cause diagnostic difficulties [Khan et al 2008, Ito et al 2009].
- ***PITX2.*** Perveen et al [2000]
- ***PITX3.*** Semina et al [1998]
- **Unknown.** Ansari et al [2016] could not identify the cause of aniridia in 20 individuals despite *PAX6*, *FOXC1*, and *PITX2* sequence analysis, FISH, and aCGH, suggesting there may be further genetic heterogeneity with potentially new disease loci and/or novel mutational mechanisms.

**Rieger anomaly,** a form of anterior segment mesenchymal dysgenesis, is characterized by severe iris atrophy, corectopia (displaced pupils), iris holes, and, frequently, childhood-onset glaucoma. Rieger anomaly may be distinguished from aniridia by the presence of posterior embryotoxon (visible Schwalbe's line seen as a white line just inside the corneal limbus) with attached iris strands, relatively good visual acuity, and the absence of nystagmus or foveal abnormality.

**Iris coloboma** is a developmental defect resulting in a focal absence of the iris and a keyhole-shaped pupil; the rest of the iris is normal. Chorioretinal coloboma may be associated. Most iris colobomas are not associated with reduced visual acuity or nystagmus unless accompanied by a large posterior coloboma that involves the optic nerve and fovea; such large chorioretinal colobomas are apparent on fundoscopic examination.

**Gillespie syndrome** (OMIM 206700), characterized by partial iris hypoplasia, cerebellar ataxia, and intellectual disability, can be distinguished from aniridia by a characteristic iris configuration in Gillespie syndrome showing a scalloped pupillary edge with iris strands extending onto the anterior lens surface [Nelson et al 1997]. In five simplex cases of Gillespie syndrome (i.e., a single occurrence in a family), three were found to have biallelic *ITPR1* pathogenic variants and two were found to have a *de novo* heterozygous *ITPR1* pathogenic variant [Gerber et al 2016].

**Oculocutaneous albinism (OCA)** and **ocular albinism** typically present in early infancy with nystagmus but a structurally complete iris, typical diffuse iris transillumination (resulting from reduced pigment in the iris pigment epithelium), hypopigmented fundus, and, in the case of OCA, skin and hair hypopigmentation, which distinguish these disorders from aniridia (see Oculocutaneous Albinism Type 4 and Oculocutaneous Albinism and Ocular Albinism Overview).

The other causes of nystagmus and poor vision in infancy (e.g., retinal dysplasia, retinal dystrophy, congenital cataracts, optic nerve hypoplasia, congenital infections) lack the iris changes seen in aniridia.

Causes of partial or complete absence of iris tissue in adults include trauma, prior ocular surgery, and the iridocorneal endothelial syndromes. The age at onset, medical history, and absence of other ocular features in aniridia should prevent diagnostic confusion with aniridia.

# Management

## Evaluation Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with aniridia (whether isolated or part of WAGR syndrome), the following are recommended:

- Evaluation of visual acuity (not easily performed in infants) and documentation of the degree of iris tissue deficiency, and the presence of foveal and optic nerve hypoplasia in order to predict future visual function.
- Evaluation for the degree of involvement of the cornea and lens and measurement of intraocular pressure, as they are potentially treatable causes of further visual reduction; however, treatable changes may not appear until later in life.
- Consultation with a clinical geneticist and/or genetic counselor

To establish the extent of disease and needs in an individual diagnosed with *W*ilms tumor-*a*niridia-*g*enital anomalies-*r*etardation (WAGR) syndrome, the following are recommended:

- Evaluation by a pediatrician to assess growth and feeding
- Evaluation for Wilms tumor
- Evaluation by a urologist for urogenital abnormalities
- Developmental assessment

## Treatment of Manifestations

**Aniridia.** Simple measures are often the most important:

- Regular eye examinations and correction of refractive errors. Refractive errors range from high myopia through emmetropia to high hypermetropia. Spectacle correction of refractive errors is usually

recommended as use of contact lenses can be difficult in the presence of keratopathy and reduced tear production.
- Tinted or photochromic lenses to reduce light sensitivity associated with the large pupillary aperture. Colored, tinted, or artificial pupil contact lenses may reduce light sensitivity or restore a more normal appearance to the eye but, as above, may be difficult to wear because of a poor ocular surface and tear film.
- Occlusion therapy in childhood for anisometropic amblyopia or strabismic amblyopia
- Optical low-vision aids and other devices such as closed-circuit television systems to help adults and children of school age
- Advice and help with schooling
- Social support

Note: Corrective surgery for strabismus can be undertaken to improve alignment and appearance but will not result in improved visual function.

**Lens.** Cataract extraction can significantly improve visual acuity in those with severe lens opacities. It should be remembered that in aniridia visual improvement after surgery is limited by foveal hypoplasia; thus, mild to moderate lens opacities may not require surgery:

- Children rarely require surgery (lensectomy).
- In adults, phacoemulsification and intraocular lens implantation can improve visual function if the cataract is severe.

Note: (1) A significant number of individuals with aniridia have poor zonular stability, which increases the risk for intraoperative complications and influences the choice of surgical technique and options for intraocular lens (IOL) implantation [Schneider et al 2003]. (2) The use of various types of black diaphragm aniridic IOLs may reduce glare or light sensitivity but are associated with a higher rate of surgical complications [Reinhard et al 2000, Menezo et al 2005, Pozdeyeva et al 2005].

**Intraocular pressure**

- Glaucoma is usually initially treated with topical anti-glaucoma medication.
- Surgery is reserved for eyes that do not respond to medical therapy:
  - Trabeculectomy with or without antimetabolites (e.g., 5-fluorouracil, mitomycin C) is often used but is associated with a higher risk of treatment failure than that seen in individuals with primary glaucoma who undergo the same treatment.
  - Drainage tube surgery (with or without antimetabolites) or cyclodiode laser treatment may be necessary in refractory cases; however, this treatment is increasingly being undertaken as a primary procedure [Khaw 2002, Kirwan et al 2002, Arroyave et al 2003, Lee et al 2010].

Note: (1) Glaucoma presenting in infancy is more difficult to treat. Medical treatment is generally ineffective and surgery is required. Goniotomy and trabeculotomy have a low success rate, but trabeculectomy with or without antimetabolites is often successful [Nelson et al 1984, Okada et al 2000, Khaw 2002]. (2) While goniosurgery has been suggested as a preventive measure, glaucoma never develops in a significant proportion of those with aniridia [Swanner et al 2004].

**Cornea**

- Ocular surface disease can be treated medically using lubricants, mucolytics, and punctal occlusion, which may help slow the progression of sight-threatening corneal changes. Note: Drops without preservatives are often required to avoid preservative-related ocular surface toxicity.
- When corneal opacification causes significant visual reduction, penetrating keratoplasty (PK) may be considered; however, in the presence of the significant limbal stem cell deficiency observed in aniridia, PK alone has a poor prognosis [Tiller et al 2003].

- Limbal stem cell transplantation alone, preceding or concurrent with keratoplasty, may be undertaken but requires an allograft as both eyes are usually affected. This may take the form of a cultured stem cell sheet or a limbal tissue transplant [Lee et al 2008, Pauklin et al 2010]. However, this therapy is associated with a high risk of failure, and lifelong systemic immunosuppression may be required to prevent rejection. Whether the use of cultured oral mucous membrane cells may have a beneficial role is as yet uncertain.

**Aniridic fibrosis syndrome.** Surgical intervention is recommended at the first sign of aniridic fibrosis syndrome [Tsai et al 2005].

**Wilms tumor.** See Wilms Tumor Predisposition overview.

**Genital abnormalities.** This may need specialist care for functional and cosmetic management including endocrine therapy and surgical correction (e.g., hypospadias repair). There may be fertility issues that require support or active management.

**Developmental delay / intellectual disability.** There are a range of developmental, intellectual, psychiatric, and behavioral issues, as well as the challenges of visual impairment. Children may require:

- Special educational support including extra or different teaching resources and a specialized educational setting, specialist teachers of the visually impaired, educational psychologists, and formal statements of educational needs;
- Involvement of a pediatrician and sometimes a pediatric psychiatrist.

## Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

**Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

**Ages 3-5 years.** In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

**Ages 5-21 years**

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

**All ages.** Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.

- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

### Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

## Surveillance

### Aniridia

**Amblyopia and refractive error.** Children younger than age eight years should be monitored every four to six months for refractive errors and detection and treatment of incipient or actual amblyopia (strabismic, refractive, or sensory). Glasses and other visual aids should be provided to optimize access to educational materials.

**Detection of later-onset eye pathology.** Individuals with aniridia should have an annual ophthalmology review to detect issues such as corneal changes, raised intraocular pressure, and cataracts.

**Glaucoma.** Individuals with aniridia should undergo annual glaucoma screening throughout life including:

- Measurement of intraocular pressure;
- Optic disc examination;
- Visual field assessment when possible.

Note: Assessment of the optic disc and visual field may be difficult in the presence of media opacities and nystagmus. Optic disc photography is a useful method of monitoring optic disc changes.

**Aniridic fibrosis syndrome.** Individuals with aniridia with a history of multiple ocular procedures (penetrating keratoplasty, IOLs, and drainage tube insertion) should be monitored for aniridic fibrosis syndrome [Tsai et al 2005].

### WAGR Syndrome

**Wilms tumor.** Children with aniridia and a *WT1* deletion require renal ultrasound examinations every three months and follow up by a pediatric oncologist until they reach age eight years. See Wilms Tumor Predisposition. (Those without deletion of the *WT1* locus are at very low risk for Wilms tumor and do not require such screening [Grønskov et al 2001, Muto et al 2002].)

**Urogenital abnormalities** require follow up as per the treating urologist and/or endocrinologist.

**Renal function.** Because of the increased risk for renal impairment in WAGR syndrome, lifelong evaluation of renal function is recommended for those with WAGR syndrome, especially those with bilateral Wilms tumor [Breslow et al 2005], by annual monitoring of blood pressure and urinalysis for proteinuria beginning in early adolescence. Note that this monitoring is not necessary for individuals in whom genetic testing has excluded a *WT1* deletion.

**Hearing.** Children with WAGR syndrome and isolated aniridia may have abnormal hearing despite a normal audiogram; thus, detailed audiologic evaluation is recommended [Bamiou et al 2007].

Developmental progress and educational needs require regular monitoring.

Provide behavioral assessment for anxiety, ADHD, and aggressive or self-injurious behavior as needed.

## Agents/Circumstances to Avoid

It has been suggested that intraocular surgery may increase the likelihood of (or exacerbate existing) keratopathy [Edén et al 2010], and repeated intraocular surgery does predispose to the rare but severe aniridic fibrosis syndrome. Patients should therefore be counseled about these risks before undertaking such surgery.

## Evaluation of Relatives at Risk

Early clarification of the genetic status of infants who are offspring or sibs of an individual with *PAX6*-related isolated aniridia (by either an eye examination or molecular genetic testing for the *PAX6* variant in the family) is recommended in order to identify those who would benefit from prompt treatment and surveillance of complications of aniridia.

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

## Therapies Under Investigation

Ongoing research is investigating the role and success of limbal stem cell transplantation and ocular mucous membrane cell transplantation for keratopathies associated with limbal stem cell failure, including aniridia [Menzel-Severing et al 2013, Polisetti & Joyce 2013].

A Phase II randomized, double-masked, placebo-controlled study of ataluren in individuals with aniridia caused by pathogenic nonsense variants in *PAX6* is under way (ClinicalTrials.gov Identifier: NCT02647359). This is based on preclinical evidence that the small-molecule drug ataluren can effectively suppress the nonsense mutation in the *Pax6* mouse model, generating full-length functional protein that reversed the developmental defect following postnatal drug administration [Gregory-Evans et al 2014, Wang et al 2017].

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.

# 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

Isolated aniridia and WAGR syndrome are inherited in an autosomal dominant manner.

- **Isolated aniridia** is associated with a pathogenic variant in *PAX6* or deletion of a regulatory region controlling *PAX6* expression.
- **WAGR syndrome** is associated with contiguous-gene deletions including *PAX6* and *WT1*.

# Risk to Family Members

## Isolated Aniridia

**Parents of a proband**

- Approximately 70% of individuals diagnosed with isolated aniridia have an affected parent (i.e., familial aniridia) [Valenzuela & Cline 2004].
- Approximately 30% of affected individuals have no family history of aniridia (i.e., simplex aniridia) and have the disorder as a result of a *de novo PAX6* pathogenic variant or deletion of a regulatory region controlling *PAX6* expression. (Note: Simplex aniridia is also referred to as "sporadic aniridia," which may be misleading as "sporadic" implies that a disorder is not expected to recur in a family.)
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo PAX6* pathogenic variant or regulatory region deletion (i.e., neither parent is known to have aniridia). Examination of both parents for evidence of minor degrees of iris hypoplasia or reduced visual acuity caused by foveal hypoplasia is recommended.
- If the *PAX6* pathogenic variant or regulatory region deletion identified in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (parental germline mosaicism for *PAX6* intragenic variants has been reported on rare occasions [Grønskov et al 1999]).
- The family history of some individuals diagnosed with isolated aniridia may appear to be negative because of failure to recognize the disorder in family members (severity of the phenotype may vary greatly among family members). Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

**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 has isolated aniridia or has an identifiable *PAX6* regulatory region pathogenic variant, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband is low.
- If the *PAX6* alteration 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 [Grønskov et al 1999].

**Offspring of a proband.** Each child of an individual with isolated aniridia has a 50% chance of inheriting the causative genetic alteration and developing aniridia.

Note: In rare instances of mosaicism for the *PAX6* pathogenic variant in the proband, the risk to offspring may be lower [Robinson et al 2008].

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

## WAGR Syndrome

**Parents of a proband.** WAGR syndrome caused by a contiguous-gene deletion that includes *PAX6* and *WT1* usually occurs *de novo*; however, rarely an asymptomatic parent may be mosaic for such a deletion; thus, it is appropriate to offer to both parents molecular genetic testing that can detect the deletion detected in the proband.

**Sibs of a proband.** If the proband has a *de novo* contiguous-gene deletion and neither parent has evidence of mosaicism for the deletion, the risk to sibs is no greater than that in the general population.

**Offspring of a proband.** Individuals with WAGR syndrome caused by a cytogenetic deletion generally do not reproduce.

## 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 genetic alteration 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/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 have isolated aniridia and to parents of affected individuals.

## Prenatal Testing and Preimplantation Genetic Testing

Prenatal testing for a pregnancy at increased risk for *PAX6*-related aniridia and preimplantation genetic testing are possible if:

- A *PAX6* pathogenic variant or regulatory region pathogenic variant has been identified in a proband with isolated aniridia [Churchill et al 2000];
- A deletion of *PAX6* and *WT1* has been identified in a proband with WAGR syndrome.

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.*

- **Aniridia Foundation International (AFI)**
  P.O. Box 41
  Manitowish Waters WI 54545
  **Phone:** (901) 409-1600
  www.make-a-miracle.org

- **Aniridia Network UK**
  22 Cornish House
  Adelaide Lane
  Sheffield S3 8BJ
  United Kingdom
  **Phone:** 07792 867 949
  **Email:** info@aniridia.org.uk
  www.aniridia.org.uk

- **International WAGR Syndrome Association**
  **Email:** Reachingout@wagr.org
  http://www.wagr.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.** PAX6-Related Aniridia: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *PAX6* | 11p13 | Paired box protein Pax-6 | PAX6 @ The Human Genetics Unit Edinburgh U.K. | PAX6 | PAX6 |

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 PAX6-Related Aniridia (View All in OMIM)

| | |
|---|---|
| 106210 | ANIRIDIA 1; AN1 |
| 194070 | WILMS TUMOR 1; WT1 |
| 194072 | WILMS TUMOR, ANIRIDIA, GENITOURINARY ANOMALIES, AND IMPAIRED INTELLECTUAL DEVELOPMENT SYNDROME; WAGR |
| 607102 | WT1 TRANSCRIPTION FACTOR; WT1 |
| 607108 | PAIRED BOX GENE 6; PAX6 |

## Molecular Pathogenesis

*PAX6* belongs to the PAX (paired box) family of genes that code for highly conserved DNA-binding proteins believed to be important in controlling organogenesis by altering expression of other genes [van Heyningen & Williamson 2002].

**Gene structure.** *PAX6* occupies 22 kb. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. The longest transcript encoding the longest isoform is NM_000280.4. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** More than 470 unique *PAX6* pathogenic variants have been identified, more than 90% of which are predicted to disrupt transcription or translation [Prosser & van Heyningen 1998, Tzoulaki et al 2005, Richardson et al 2016]:

- Approximately 60% are intragenic loss-of-function variants that introduce a premature termination codon and (occasionally) variants of up- or downstream regulatory sequences. This is generally associated with more severe disease including a high incidence of complications [Prosser & van Heyningen 1998, Crolla & van Heyningen 2002, Tzoulaki et al 2005, Hingorani et al 2009].
- Approximately 25% are missense variants that have been detected in less severe forms of aniridia, and that may code for nearly complete loss of protein function, or are associated with other ocular phenotypes such as isolated foveal hypoplasia [Azuma et al 1998, Vincent et al 2003, Chauhan et al 2004, Tzoulaki et al 2005, Hingorani et al 2009].
- A small percentage are C-terminal extension (CTE) variants (e.g., variants in the stop codon that extend the protein), such as c.1267dupT, which has been reported more than 20 times, are associated with more severe aniridia phenotypes, sometimes with retinal changes [Hingorani et al 2009; Richardson et al 2016].

Four CpG dinucleotides in exons 8, 9, 10, and 11 are the most common sites for pathogenic variants, accounting for 21% of all reported pathogenic variants [Tzoulaki et al 2005]. Large deletions that may involve other genes (e.g., *WT1*) also produce aniridia.

Many pathogenic variants have been reported in *PAX6*, both in aniridia and in related ocular phenotypes including Peters anomaly, foveal hypoplasia, and optic nerve anomalies:

- Of the *PAX6* pathogenic variants known to cause aniridia, most lead to loss of protein function and comprise nonsense variants (39%), splice variants (13%), frameshifting deletions and insertions (25%), in-frame insertions and deletions (6%), missense variants (12%), and run-on variants (5%) [Prosser & van Heyningen 1998, Tzoulaki et al 2005].
- Of the approximately 30 known pathogenic variants for non-aniridia eye disorders, 69% are missense variants [Tzoulaki et al 2005].

Reduction of expression of alternatively spliced PAX6 protein isoforms can also cause an altered or less severe phenotype [Azuma et al 1999, Vincent et al 2003, Chauhan et al 2004].

**Table 3.** *PAX6* Pathogenic Variants Discussed in This *GeneReview*

| DNA Nucleotide Change | Predicted Protein Change | Reference Sequences |
|---|---|---|
| c.1267dupT | p.Ter423LeuextTer36 | NM_000280.4<br>NP_000271.1 |

Variants listed in the table have been provided by the authors. *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.

**Normal gene product.** *PAX6* encodes the PAX6 protein, a 422-amino-acid protein (NP_000271.1) that acts as a transcription factor. PAX6 contains a paired domain and a paired-type homeodomain, both with DNA-binding capability, separated by a lysine-rich linker region. A C-terminal proline, serine, and threonine-rich (PST) domain acts as a transcriptional activator.

PAX6 protein is thought to act as the major controller of ocular development during embryogenesis by effects on cellular proliferation, differentiation, migration, and adhesion; several target genes have been identified [van Heyningen & Williamson 2002]. PAX6 protein expression continues in the adult retina, lens, and cornea and may help maintain good ocular health [Koroma et al 1997, van Heyningen & Williamson 2002].

Various isoforms of PAX6 protein are derived through alternative splicing (PAX6-ex12, PAX6-5a,6', PAX6-5a). The ratios of these isoforms may be critical to normal ocular development [Singh et al 2002].

**Abnormal gene product.** Heterozygous pathogenic variants of *PAX6* appear to disturb ocular morphogenesis, resulting in aniridia and related ocular phenotypes, and also may produce mild central nervous system defects [Sisodiya et al 2001, Free et al 2003, Ellison-Wright et al 2004, Valenzuela & Cline 2004]. Homozygous or compound heterozygous loss of *PAX6* function leads to anophthalmia and central nervous system defects, which are often fatal [Hodgson & Saunders 1980, Glaser et al 1994, Schmidt-Sidor et al 2009].

**WAGR syndrome** is caused by either cryptic or cytogenetically visible deletions involving varying amounts of 11p that include band 11p13 with *PAX6* and neighboring genes. The loss of *WT1* produces genitourinary and renal abnormalities and predisposes to Wilms tumor, which results from loss of heterozygosity. Deletion of one copy of *PAX6* causes aniridia.

Yamamoto et al [2014] describe an individual with an unusual deletion split into two regions on chr11p13 – a 2.2-Mb and a 10.5-Mb deletion with *PAX6* and *PRRG4* preserved at normal copy number between them – who

did not have WAGR or autistic behavior. They suggest that haploinsufficiency of *PAX6* or *PRRG4* is responsible for intellectual disability and autistic features associated with WAGR.

# Chapter Notes

## Revision History

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