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Aniridia

[*Includes: Isolated Aniridia, Wilms Tumor-Aniridia-Genital Anomalies-Retardation (WAGR) Syndrome*]

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Summary

Disease characteristics. Aniridia is characterized by complete or partial iris hypoplasia with associated foveal hypoplasia resulting in reduced visual acuity and nystagmus presenting in early infancy. Frequently associated ocular abnormalities, often of later onset, include cataract, glaucoma, and corneal opacification and vascularization. Aniridia may occur either as an isolated ocular abnormality without systemic involvement, caused by mutation of *PAX6* or deletion of a regulatory region controlling its expression, or as part of the Wilms tumor-aniridia-genital anomalies-retardation (WAGR) syndrome, with a deletion of 11p13 involving the *PAX6* (aniridia) locus and the adjacent *WT1* (Wilms tumor) locus. Individuals with deletion of PAX6 and WT1 have up to 50% risk of developing Wilms tumor.

Diagnosis/testing. Aniridia is diagnosed by clinical examination. Sequence analysis of the *PAX6* coding region and deletion testing to identify *PAX6* exonic or whole-gene deletions are used to identify the disease-causing mutation in those with isolated aniridia. High-resolution cytogenetic testing at the 600-650-band level to detect deletions involving 11p13 and FISH testing or deletion testing to detect deletions of *PAX6* and *WT1* are used to identify the underlying disease-causing mechanism in those with the diagnosis of WAGR syndrome. All testing described here is clinically available.

Management. *Treatment of manifestations*: Aniridia is treated with spectacle correction of refractive errors, tinted or photochromic lenses to reduce light sensitivity, occlusion therapy for amblyopia, and low-vision aids such as closed-circuit television. Cataract extraction may improve visual acuity. Glaucoma is initially treated with topical anti-glaucoma medication; refractory cases may require surgery (trabeculectomy or drainage tube surgery) or cyclodiode treatment. Corneal disease is treated with lubricants, mucolytics, and punctal occlusion. Aniridic fibrosis syndrome is treated with surgery. *Surveillance*: annual glaucoma screening throughout life including measurement of intraocular pressure, optic disc examination, and, when possible, visual field assessment. Monitoring for aniridic fibrosis syndrome with slit lamp examination in those with multiple previous intraocular surgeries. Renal ultrasound examination every three months for children with aniridia and a WT1 deletion. Lifelong evaluation of renal function in individuals with WAGR syndrome, especially those with bilateral Wilms tumor. *Testing of relatives at risk*: An eye examination in infancy is recommended for offspring and sibs of individuals with aniridia.

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Genetic counseling. Isolated aniridia is inherited in an autosomal dominant manner. Most individuals with isolated aniridia have an affected parent; however, some may have isolated aniridia as the result of a *de novo* gene mutation. Each offspring of an individual with isolated aniridia has a 50% chance of inheriting the *PAX6* mutation and developing aniridia. WAGR syndrome caused by a contiguous gene deletion usually occurs *de novo*; WAGR syndrome caused by a cytogenetically visible deletion may be *de novo* or may result from transmission by a parent with a balanced chromosome rearrangement. Prenatal testing is available for pregnancies at increased risk for isolated aniridia if the disease-causing mutation of an affected family member has been identified and for pregnancies at increased risk for WAGR syndrome if a contiguous gene deletion or a cytogenetically visible deletion has been confirmed in the proband.

Diagnosis

Clinical Diagnosis

Aniridia is characterized by complete or partial iris hypoplasia with associated foveal hypoplasia resulting in reduced visual acuity and nystagmus presenting in early infancy. Frequently associated ocular abnormalities, often of later onset, include cataract, glaucoma, and corneal opacification and vascularization.

Techniques used to identify the ocular abnormalities of aniridia

- **Slit lamp examination.** Partial or complete iris absence, iris translucency, or abnormal architecture and pupillary abnormalities may be seen; corneal opacification and vascularization, cataract, and glaucoma can also be detected if present.
- **Iris fluorescein angiography** may identify subtle iris hypoplasia but is rarely used clinically.
- **Optical coherence tomography (OCT)** may be used to document foveal hypoplasia in atypical cases. Although OCT is difficult to perform in the presence of nystagmus, useful images can be obtained with persistence.
- **High-frequency ultrasound biomicroscopy (UBM).** In infants with corneal opacity or severe corneal edema resulting from associated congenital glaucoma, high-frequency anterior segment ultrasound examination can demonstrate iris hypoplasia and/or absence [Nischal 2007].

Aniridia may occur as **one** of the following:

- **Isolated aniridia** without systemic involvement caused by mutation of *PAX6* or deletion of a regulatory region controlling *PAX6* expression

  Note: Isolated aniridia may occur in individuals with a positive family history consistent with autosomal dominant inheritance (familial aniridia: 70% of all individuals with aniridia) and in individuals with no family history of aniridia (simplex aniridia, commonly referred to as "sporadic aniridia": 30% of individuals with aniridia) [Valenzuela & Cline 2004].

  OR

- The **W**ilms tumor-**a**niridia-**g**enital anomalies-**r**etardation (WAGR) syndrome

WAGR syndrome may be diagnosed on the following findings:

- A visible deletion of 11p13 found on cytogenetic testing

  OR

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- A submicroscopic deletion involving the *PAX6* (aniridia) locus and the adjacent *WT1* (Wilms tumor) locus found on FISH testing or heterozygosity testing

  OR

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

  Note: (1) Because Wilms tumor, mental retardation, and behavioral abnormalities are unlikely to be evident in a very young child with WAGR syndrome, the clinical diagnosis of WAGR syndrome usually cannot be established or ruled out until a child has passed through the age of risk for these manifestations. (2) The external genitalia are usually normal in females with WAGR syndrome [Fischbach et al 2005].

Testing

Cytogenetic testing. High-resolution cytogenetic testing at the 600-650-band level detects deletions involving 11p13 in up to 20% of individuals with no family history of aniridia.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes

- Mutations or deletions in *PAX6* or its control elements are associated with isolated aniridia.
- Contiguous gene deletions including *PAX6* and *WT1* are associated with aniridia and the risk of one or more additional manifestations of WAGR.

Clinical testing

WAGR syndrome

- **FISH testing.** A probe or probes spanning *PAX6*, *WT1*, the regions flanking *PAX6*, and the intervening sequence between *PAX6* and *WT1* can be used:
  - To detect cryptic deletions and contiguous gene deletions in individuals with no family history of aniridia and normal cytogenetic studies

    AND
  - To confirm, when necessary, deletion of *WT1* in individuals with a cytogenetic abnormality involving 11p13 [Crolla & van Heyningen 2002].
- **Deletion testing.** Using a variety of methods including quantitative polymerase chain reaction (qPCR)/real-time PCR (rt-PCR), and multiplex ligation-dependent probe amplification (MLPA), deletions of *PAX6* and *WT1* can be identified in individuals with WAGR syndrome.

Isolated aniridia

- **Sequence analysis.** Sequence analysis can be used to identify mutations in or near *PAX6* associated with isolated aniridia [Robinson et al 2008].

- **Deletion testing.** Using a variety of methods including qPCR/rt-PCR, and MLPA, exonic or whole-gene deletions of *PAX6* can be detected in 39% of individuals with isolated aniridia [Robinson et al 2008].

Table 1 summarizes molecular genetic testing for this disorder [Robinson et al 2008].

Table 1. Genetic Testing of Aniridia by Phenotype and Family History

Phenotype	Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Phenotype and Test Method		Test Availability
				Family History		
				Negative	Positive	
WAGR syndrome [1]	*PAX6* and contiguous genes	High-resolution cytogenetic testing	Cytogenetic deletion 11p13	57%	NA	Clinical
	PAX6 and *WT1*	FISH	Submicroscopic deletion	14%	NA	Clinical Testing
		Deletion testing [3]	Whole-gene deletions	Unknown	NA	
Isolated aniridia [2]	*PAX6*	Sequence analysis of coding region	Sequence alterations	55%	62.5%	Clinical Testing
		Deletion testing [3]	Exonic deletions and deletions of control regions	22%	17%	

NA= Not applicable

1. **W**ilms tumor, **a**niridia **g**enital anomalies, mental **r**etardation. Note: In young individuals, Wilms tumor and mental retardation may not be evident; in females, external genitalia are often normal.

2. Isolated aniridia: aniridia without systemic involvement

3. Testing that identifies deletions/duplications not detectable by sequence analysis of genomic DNA; a variety of methods including qPCR, rtPCR, MLPA, and array CGH (see Testing) may be used.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Establishing the diagnosis of isolated aniridia vs WAGR

Evaluate the proband with cytogenetic, FISH testing, and/or deletion testing of *PAX6* and *WT1* first when the proband is:

- An infant with aniridia who is a simplex case (i.e., a single occurrence in the family)

  OR

- An older individual with aniridia and mental retardation and/or Wilms tumor and/or genital anomalies.

Identification of deletion of *PAX6* and *WT1* by cytogenetic studies, FISH testing, or deletion testing confirms the diagnosis of WAGR syndrome.

Evaluate the proband with *PAX6* sequence analysis and/or *PAX6* deletion testing first when the proband:

- Is known to have isolated aniridia (either because s/he has exceeded the age of risk for Wilms tumor and mental retardation or s/he has a positive family history of isolated aniridia)

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OR

- Has no family history of aniridia, a normal karyotype, and no deletion of *WT1* by FISH testing or deletion testing.

Identification of a *PAX6* sequence alteration, a *PAX6* exonic deletion, or deletions of *PAX6* control regions confirms the diagnosis of isolated aniridia.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

***PAX6* mutations.** Missense mutations 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 Ocular Phenotypes Caused by *PAX6* Mutations

Ocular Phenotype	Manifestations
Keratitis	Limbal stem cell deficiency with vascularization and opacification of the cornea ± foveal hypoplasia
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 with neurodevelopmental anomalies	Absent or highly malformed central chorioretinal area, variable neurologic abnormalities (e.g., cerebellar syndrome, cortical atrophy, low IQ, absent pineal gland)

From pax6.hgu.mrc.ac.uk

1. *PAX6* mutations have not been detected in most individuals with Peters anomaly [Churchill et al 1998, Chavarria-Soley et al 2006, Dansault et al 2007].

Individuals with two *PAX6* loss-of-function mutations. In the rare cases of a homozygous *PAX6* mutation, severe craniofacial abnormalities, anophthalmia, absent or malformed nose, absent adrenal glands, central nervous system malformations, and fetal or neonatal death have occurred [Hodgson & Saunders 1980, Glaser et al 1994].

Clinical Description

Natural History

Aniridia is a panocular 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. Other abnormalities include corneal changes, glaucoma, cataract, lens subluxation, strabismus, and optic nerve coloboma and hypoplasia.

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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 six weeks of age). 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 problems, 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 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. 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. 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 aniridia, but the exact prevalence is unknown. The onset of glaucoma is usually in later childhood or adulthood; glaucoma in infancy is rare.

Cornea. Keratopathy (corneal degeneration) is a relatively late manifestation with multifactorial causes including limbal stem cell abnormalities [Ramaesh et al 2005]. Changes vary from mild peripheral vascularization to pancorneal 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].

Fovea. Foveal hypoplasia is usually present. Findings include reduced foveal reflex, macular hypopigmentation, and crossing of the usual foveal avascular zone by retinal vessels.

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

Aniridic fibrosis syndrome. Patients with aniridia with a history of multiple ocular procedures (penetrating keratoplasty, intraocular lenses (IOLs), and drainage tube insertion) may 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].

Central nervous system. Individuals with isolated aniridia may show reduced olfaction and cognition, behavioral problems, or developmental delay. Central nervous system abnormalities (including absence or hypoplasia of the anterior commissure, abnormalities of grey matter in the anterior cingulate cortex, cerebellum, 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

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2003, Mitchell et al 2003, Ellison-Wright et al 2004, Valenzuela & Cline 2004, Bamiou et al 2007].

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].

WAGR syndrome. Individuals with cytogenetically visible deletions of 11p13 or cryptic deletions of *PAX6* and *WT1* may develop WAGR syndrome: **W**ilms tumor, **a**niridia, **g**enitourinary abnormalities and mental **r**etardation [Fischbach et al 2005]:

- **Wilms tumor** risk for individuals with a cytogenetically visible deletion of 11p13 or a submicroscopic deletion that involves *PAX6* and *WT1* is probably as high as 50%. Individuals with WAGR syndrome are more likely than those with isolated Wilms tumor to develop bilateral tumors and have an earlier age of diagnosis and a more favorable tumor histology with better prognosis.
- **Aniridia** is almost universally present in individuals with such a deletion and typically is severe. However, WAGR without aniridia has been described.
- **Genitourinary abnormalities** include cryptorchidism (most commonly, in 60% of males), uterine abnormalities, hypospadias, ambiguous genitalia, streak ovaries, urethral strictures, ureteric abnormalities, and gonadoblastoma.
- **Mental retardation and behavioral abnormalities** in WAGR syndrome are highly variable:
  - Seventy percent of individuals with WAGR syndrome have mental retardation (defined as IQ <74); other individuals with WAGR syndrome can have normal intellect without behavior problems.
  - Behavioral abnormalities include attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (see Autism Overview), 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.
- **End-stage renal disease (ESRD).** The risk of later ESRD is significant, relating to Wilms tumor and its surgery, focal segmental glomerulosclerosis, and occasionally renal malformation. The rate of ESRD 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].
- **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].

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).

Early studies recognized that 30% of individuals with aniridia with no family history of aniridia developed Wilms tumor within the first five years of life; subsequent studies revealed that the risk may be lower [Gronskov et al 2001]. It is now known that these individuals have WAGR syndrome caused by a contiguous gene deletion encompassing both *PAX6* and the nearby

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Wilms tumor suppressor gene *(WT1*). Absence of one *WT1* allele in the germline in these individuals leads to a high risk (~45%) of Wilms tumor occurring through somatic mutation that results in loss of heterozygosity (LOH) in a single differentiating kidney cell.

Genotype-Phenotype Correlations

Isolated aniridia. *PAX6* missense mutations (often in the paired domain) tend to produce atypical or variable-phenotype aniridia or related disorders (see Table 2) such as foveal hypoplasia, autosomal dominant keratitis, developmental abnormalities of the optic nerve, and Peters anomaly, sometimes associated with neurodevelopmental abnormalities.

PAX6 haploinsufficiency through loss-of-function intragenic mutations (often premature termination codons), larger deletions, or occasional chromosomal rearrangements at nearby regulatory elements produces classic aniridia [Kleinjan & van Heyningen 1998, Prosser & van Heyningen 1998, Gronskov 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].

Although the phenotype can be variable within a family, individuals usually show little difference between the two eyes. The causes for this variation in phenotype among individuals with the same mutation are unknown [Negishi et al 1999].

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 LOH. Deletion of one *PAX6* gene causes aniridia. The exact gene loss responsible for mental retardation is uncertain [Fischbach et al 2005].

Penetrance

Penetrance is 100%.

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 unknown.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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.

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Gillespie syndrome, characterized by partial iris hypoplasia, cerebellar ataxia, and mental retardation, 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].

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 1, Oculocutaneous Albinism Type 2, Oculocutaneous Albinism Type 4, and X-Linked Ocular Albinism).

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 iridocornealendothelial (ICE) syndromes. The age at onset, medical history, and lack of other ocular features of aniridia should prevent diagnostic confusion with aniridia.

Management

Evaluation Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with aniridia, the following are recommended:

- Evaluation of visual acuity (not easily performed in infants), the degree of iris tissue deficiency, the presence of foveal and optic nerve hypoplasia in order to predict future visual function
- Evaluation for the presence and degree of corneal involvement, cataract, and glaucoma, as they are potentially treatable causes of further visual reduction; however, they may not appear until later in life.

Treatment of Manifestations

Aniridia. During childhood, 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
- Occlusion therapy 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

Lens. Cataract extraction can significantly improve visual acuity in those patients 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:

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- Children rarely require surgery (lens aspiration or lensectomy).
- In adults, phacoemulsification can be successful.

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 IOL implantation [Schneider et al 2003]. (2) The use of various types of black diaphragm aniridic IOLs may reduce glare or light sensitivity but may be associated with a slightly higher rate of surgical complications [Reinhard et al 2000, Menezo et al 2005, Pozdeyeva et al 2005].

Intraocular pressure

- Glaucoma is 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 the operation of choice.
  - Drainage tube surgery (with or without antimetabolites) or cyclodiode laser treatment may be necessary in refractory cases [Khaw 2002, Kirwan et al 2002, Arroyave et al 2003].

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 most of those with aniridia [Swanner et al 2004].

Cornea

- Ocular surface disease can be treated medically using lubricants, mucolytics, and punctal occlusion. 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].

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

Wilms tumor. See Wilms Tumor Overview.

Surveillance

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.

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Aniridic fibrosis syndrome. Patients 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].

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

Renal function. Because of the increased risk of renal impairment in WAGR syndrome, it has been suggested that renal function be evaluated lifelong in those with WAGR syndrome, especially those with bilateral Wilms tumor [Breslow et al 2005].

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].

Testing of Relatives at Risk

It is recommended that offspring and sibs of individuals with aniridia have an eye examination in infancy.

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

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

Mode of Inheritance

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

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Risk to Family Members — Isolated Aniridia

Parents of a proband

- Most individuals diagnosed with isolated aniridia have an affected parent.
- A proband with isolated aniridia and no family history may have the disorder as the result of a *de novo* gene mutation or gene deletion.
- Because the severity of the phenotype may vary greatly among family members, recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include examination of both parents for evidence of minor degrees of iris hypoplasia or reduced visual acuity caused by foveal hypoplasia.

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* mutation, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a *PAX6* mutation cannot be detected in the DNA of either parent of the proband, germline mosaicism in a parent should be considered. Germline mosaicism for *PAX6* intragenic mutations has been reported on rare occasions [Gronskov et al 1999].

Offspring of a proband. Each child of an individual with isolated aniridia has a 50% chance of inheriting the *PAX6* mutation and developing aniridia.

Note: In rare instances of mosaicism for the *PAX6* mutation in the proband, the risk to offspring may be lower.

Risk to Family Members — WAGR Syndrome

Parents of a proband

- WAGR syndrome caused by a contiguous gene deletion that includes *PAX6* and *WT1* that is detected only by FISH testing or deletion testing usually occurs *de novo*; however, rarely an asymptomatic parent may be mosaic for such a deletion; thus, it is appropriate to offer FISH testing or deletion testing to both parents.
- In individuals with WAGR syndrome caused by a cytogenetically visible deletion, it is appropriate to offer cytogenetic testing to both parents to determine if either parent has a balanced chromosome rearrangement.

Sibs of a proband

- If a parent has a balanced chromosome rearrangement, the risk to the sibs is increased depending on the nature of the chromosome rearrangement.
- 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.

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Related Genetic Counseling Issues

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

Family planning

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

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal testing using fetal cells obtained by amniocentesis is usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation is available under the following circumstances:

- For pregnancies at increased risk for isolated aniridia if the disease-causing *PAX6* mutation or regulatory region deletion has been identified [Churchill et al 2000]
- For pregnancies at increased risk for WAGR syndrome caused by a cytogenetic deletion if a balanced chromosome rearrangement has been identified in a parent.
- For pregnancies at increased risk for WAGR syndrome caused by a cryptic deletion detectable by FISH or deletion testing.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which (1) the disease-causing *PAX6* mutation has been identified or (2) a chromosome rearrangement detectable by chromosome analysis or FISH has been demonstrated in a parent. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Aniridia

Gene Symbol	Chromosomal Locus	Protein Name
PAX6	11p13	Paired box protein Pax-6

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

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Table B. OMIM Entries for Aniridia

106210	ANIRIDIA, TYPE II; AN2
194070	WILMS TUMOR 1; WT1
194072	WAGR SYNDROME
607102	WILMS TUMOR 1 GENE; WT1
607108	PAIRED BOX GENE 6; PAX6

Table C. Genomic Databases for Aniridia

Gene Symbol	Locus Specific	Entrez Gene	HGMD
PAX6	PAX6	5080 (MIM No. 607108)	PAX6

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic 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]. *PAX6* is expressed in ocular, neural, nasal, and pancreatic tissue during development. Heterozygous mutations 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 loss of *PAX6* function leads to anophthalmia and central nervous system defects and is fatal [Hodgson & Saunders 1980, Glaser et al 1994].

Normal allelic variants: *PAX6* occupies 22 kb on chromosome 11p13 and contains 14 exons and 13 introns. The genomic sequence is available (www.sanger.ac.uk). Five non-pathogenic normal allelic variants are known.

Pathologic allelic variants: More than 300 *PAX6* mutations have been identified; 286 are associated with congenital eye malformations [Prosser & van Heyningen 1998, Tzoulaki et al 2005]:

- Approximately 72% are intragenic loss-of-function mutations that introduce a premature termination codon into the *PAX6* open reading frame and (occasionally) mutations of up- or downstream regulatory sequences [Prosser & van Heyningen 1998, Crolla & van Heyningen 2002, Tzoulaki et al 2005]
- Approximately 12% are missense mutations that have been detected in typical aniridia and that may code for near-to-loss-of-function protein [Azuma et al 1998, Vincent et al 2003, Chauhan et al 2004, Tzoulaki et al 2005]

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

Many mutations have been reported in *PAX6*, both in aniridia and related ocular phenotypes such as Peters anomaly, foveal hypoplasia, and optic nerve anomalies:

- Of the 257 known *PAX6* mutations causing aniridia, most lead to loss of protein function and comprise nonsense mutations (39%), splice mutations (13%), frameshifting deletions and insertions (25%), inframe insertions and deletions (6%),

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missense mutations (12%), and run-on mutations (5%) [Prosser & van Heyningen 1998, Tzoulaki et al 2005].

- Of the 29 known mutations for non-aniridia eye disorders, 69% are missense mutations [Tzoulaki et al 2005].

Normal gene product: *PAX6* encodes the PAX6 protein, a 422-amino acid protein 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: Most *PAX6* mutations cause loss of protein function. This was previously believed to occur primarily through premature protein truncation but is now hypothesized to arise from nonsense-mediated decay [Prosser & van Heyningen 1998, Tzoulaki et al 2005]. Missense mutations are believed to produce reduced-function protein, resulting in the variant ocular phenotypes or (if protein function is greatly reduced) in aniridia. 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].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Aniridia Foundation International
930 Madison Avenue Suite 314
Memphis TN 38163
Phone: 901-448-2380
Fax: 901-448-2382
Email: info@aniridia.net
www.aniridia.net

Aniridia Network International
109 Gavin Way
Colchester CO4 9FR
United Kingdom
Phone: 01206 842 742
Email: hannah@aniridia.org
www.aniridia.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 12 July 2008 (me) Comprehensive update posted to live Web site
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