



Published in final edited form as:

Expert Rev Ophthalmol. 2016 ; 11(2): 135–144. doi:10.1586/17469899.2016.1152182.

Congenital aniridia: etiology, manifestations and management

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Summary

Congenital aniridia manifests as total or partial absence of the iris caused most commonly by mutations in *PAX6*, *FOXC1*, *PITX2*, and *CYP1B1*. Recently two new genes, *FOXD3* and *TRIM44*, have also been implicated in isolated studies. We discuss the genotype-phenotype correlations for the main implicated genes. Classic aniridia is a panocular condition, which includes aniridia, cataract, corneal pannus, foveal, and optic nerve hypoplasia associated with mutations in the *PAX6* gene. Classical aniridia is due to *PAX6* mutations, while other genes contribute to aniridia-like phenotypes. We review the challenges involved in the management of aniridia, and discuss various surgical interventions. The clinical importance of defining the genotype in cases of congenital aniridia has become acutely apparent with the advent of possible therapies for classical aniridia, which are discussed.

Keywords

aniridia; congenital; aniridia-associated keratopathy; goniotomy; cataract

Aniridia is an ocular disorder in which there is total or partial hypoplasia of the iris tissue. It was first described by Barrata in 1818 [1]. In this review, we discuss the etiology, presentation, complications, management and possible future developments of this disorder.

Etiology

Aniridia may be congenital or acquired. Acquired aniridia is almost always secondary to trauma and usually unilateral [2]. Congenital aniridia is described as partial or total absence of iris, but gonioscopy almost always reveals an iris stump [3]. For congenital partial or total aniridia, mutations in the following genes have been reported; *PAX6*, *FOXC1*, *PITX2*, *CYP1B1*, *FOXD3* and *TRIM44* (Table 1).

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PAX6

This gene encodes a paired domain DNA-binding transcription factor that has been shown to be critical in eye formation and important for neural, pancreas and olfactory system development [4]. In humans, the gene is located on chromosome 11p13, the transcript encompasses 14 exons over 27.4 kb of genomic DNA, and the coding region starts from exon 4. It has two major isoforms, which are canonical Pax6 and Pax6(5a) [5], that have been shown to activate different targets [6, 7], and a paired-less form that may regulate amacrine populations in the retina [8, 9]. Apart from expression in the developing and mature eye (Figure 1), Pax6 is also expressed in the developing forebrain, gut, pineal gland, β -cells of the pancreas and olfactory epithelium [4].

Since *PAX6* is expressed in the cornea, lens, iris and retina, it is not surprising that heterozygous mutations result in a panocular condition affecting the cornea, lens, iris, retina and optic nerve (see later). Haploinsufficiency of the protein arising from deleterious mutations results in aniridia (Table 1). The *PAX6* mutation database currently reports 376 novel mutations [10], with heterozygous mutations primarily resulting in aniridia in about 90% of cases [11], where intragenic mutations account for two-third of cases and chromosomal rearrangements for one-third of cases. Ninety-four percent of all intragenic point mutations leads to either a premature termination codon (PTC), C-terminal extensions (CTE), or amino acid substitutions [12]. The importance of this will become critically clear when we discuss future developments. In a fraction of classical aniridia patients, the mutation is located outside the *PAX6* structural gene and, in particular, in its transcriptional control regions [13, 14].

Two-thirds of all aniridic cases due to *PAX6* mutation are familial displaying autosomal dominant inheritance and the remaining are sporadic [11]. Sporadic mutations arise from de novo gene mutations or deletions. Sporadic deletions of *PAX6* contiguous with *WT1* (about 700 kb apart) often lead to Wilms Tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome [15], which Wilms' tumor, aniridia, genitourinary anomalies, and intellectual disability (replacing the former term mental retardation). Wilms' tumor develops through somatic loss of both *WT1* alleles in the kidney, or more rarely the gonad; therefore, the extent of the WAGR phenotype is dependent on the length of the deletion.

FOXC1

This gene product is a member of the forkhead domain/winged helix (FHD) class of transcription factors that play essential roles in embryonic development, such as cellular differentiation and proliferation [16]. In humans, the gene is located on chromosome 6p25, contains 1 exon and spans 3.9 kb of genomic DNA. In the developing eye, *FoxC1* is expressed in the periocular mesenchyme, with later expression in the corneal stroma, sclera, conjunctival epithelium, and trabecular meshwork (Figure 1) [17]. Extra-ocular expression includes the heart, kidney, peripheral blood leukocytes, and prostate.

Mutations in this gene typically produce ocular phenotypes, but may manifest extra-ocular phenotypes such as malar hypoplasia, hypodontia, umbilical hernia and intracranial anomalies, such as cerebellar vermis hypoplasia or Dandy-Walker syndrome. Similar to

PAX6, haploinsufficiency in *FOXC1* adversely affects development of the ocular anterior segment leading to the distinct Axenfeld-Rieger syndrome (ARS; see later). The type of *FOXC1* mutations that gives rise to ARS includes missense mutations in the FHD, frameshift and nonsense mutations, and whole gene deletions/duplications. More than 50 mutations in *FOXC1* have been found to cause ARS [18]. Mutations in the *FOXC1* gene have also been identified in another eye disorder called iridogoniodysgenesis type 1, where the anterior segment of the eye is primarily involved, and is associated with underdevelopment of the iris and an elevated risk of glaucoma.

A number of mutations or deletions of *FOXC1* that results in aniridia, usually with severe glaucoma, have been reported (Table 1). The first is a case of total aniridia and subtle iris hypoplasia in a month-old female and her mother, respectively, due to a heterozygous p.Met161Lys *FOXC1* missense mutation. The second a case of aniridia from a heterozygous p.Trp152Gly missense mutation in a newborn male, and the third a case of total aniridia from homozygosity for a missense mutation, p.Pro297Ser, in a female patient. The fourth reports acquired peripheral circumferential iris degeneration from a heterozygous deletion, p.Tyr81_Pro95del, in a month old female. The fifth describes a newborn female and 6-day old male with a deletion of 1.5Mb at 6p25.3p25.2 and duplication of 46XY, dup(6)(25.1p25.3), respectively, that both encompass *FOXC1* leading to total aniridia-like symptoms in both patients.

PITX2

This gene belongs to the bicoid class of homeodomain proteins known as RIEG/PITX and its function includes development of the eye anterior segment [19], tooth development, left-right determination, early morphogenesis and arrhythmogenesis during cardiac development [20], and myogenesis [21]. The gene in humans is located at chromosome 4q25, and the coding region contains three exons spanning 5.68 kb of genomic DNA. It is expressed mainly in the neural crest tissue; therefore, it is present in the anterior segment of the developing eye (Figure 1), the developing extraocular muscles, branchial arches, developing teeth, and the maxillary, and mandibular epithelium. Its expression also extends to the umbilicus, limb buds, heart, gut, and anterior pituitary gland.

PITX2 was the first ARS gene to be identified [22]. Mutations in *PITX2* and *FOXC1* account for approximately 40% of ARS occurrences, where *PITX2* mutants usually present with ocular, dental, and umbilical anomalies and *FOXC1* mutants associate with isolated ocular or ocular, heart, and/or hearing defects. *PITX2* mutations tend to group in the homeodomain and C-terminal region, and result in complete or partial loss of function. Gain-of-function mutations, deletions of coding exons/upstream-regulatory regions, and chromosomal translocations have been reported, but are rare.

A report describes iris hypoplasia in a father with classical symptoms of ARS from a heterozygous *FOXC1* frameshift mutation p.Ala204ArgfsX111, and his wife with isolated bilateral posterior embryotoxon and iris heterochromia from a heterozygous missense mutation in the critical OAR domain (homologous to drosophila *otp*, *aristaless*, and murine *rax*) known to interact with *FOXC1* [23, 24]. Their female daughter had a severe anterior segment disorder of extruding lenses, thin cornea and severe iris hypoplasia. One other

report describes a case of severe iris hypoplasia in an individual without foveal hypoplasia due to a mutation in *PITX2* described as a IVS 2 (-1), G→C mutation (Table 1).

CYP1B1

This gene encodes the enzyme cytochrome P450, family 1, subfamily B, polypeptide 1 - a member of the cytochrome P450 superfamily that participates in oxidative biochemical reactions important to many processes in the body. It resides on chromosome 2p22 in humans and consists of three exons spanning 8.5 kb of genomic DNA, with the coding region starting from the second exon [25]. It is expressed in numerous fetal and adult tissues, including the parenchymal and stromal tissues of the brain, breast, cervix, kidney, lymph nodes, prostate, uterus, ovary, heart, placenta, lung and skeletal muscle. It is also detected in ocular tissues. Human *CYP1B1* is more highly expressed in the fetus than the adult. It is expressed in the fetal ciliary epithelium at 26 days post-conception before anterior chamber development [26]. Ocular expression is also observed in the fetal corneal epithelium, keratocytes and iris stromal cells but not in adult eyes. It is observed in the non-pigmented ciliary epithelium, iris pigmented epithelium and iris dilator muscle both in fetuses and adults. Its expression could not be detected in fetal or adult trabecular meshwork.

Mutations in *CYP1B1* occur in 87% of familial and 27% of sporadic cases of primary congenital glaucoma (PCG) worldwide [27]. It is not well understood how defects in the *CYP1B1* enzyme cause signs and symptoms of glaucoma. Cases of bilateral congenital glaucoma with aniridia due to mutations in *CYP1B1* have been previously reported (Table 1). The first was a 4-year old boy presented with bilateral buphthalmos, abnormal discoloration, central corneal scarring and absent iris. The optic nerve was cupped and pale in the right eye and retinal detachment was observed in the left eye; both due to uncontrolled glaucoma. An autozygosity scan using autoSNPa and sequencing revealed homozygosity for a previously reported *CYP1B1* mutation, p.Arg145ProfsX4. The second study involved 67 families with 46 having primary PCG. All had bilateral buphthalmos with corneal scarring, and eight additionally had mild ectropion uveae with partial aniridia. Genetic testing revealed that two of these eight had the same homozygous mutations in *CYP1B1*, specifically p.Asn252Lys. The third case involved three sisters with PCG, where two of them also had bilateral aniridia. Genetic screening showed a novel homozygous mutation in *CYP1B1*, p.Ser485Phe, for these two sisters.

FOXD3

This gene expresses another member of the family of transcription factors characterized by a forkhead/winged helix domain (FHD), but has an important role in the induction, development and migration of neural crest cells [28], formation of melanocytes, maintenance of stem cells, their ability to self-renew without differentiating, and as a marker for *embryonic* stem cells [29]. It is located on chromosome 1p31.3 in humans, and is encoded by 1 exon spanning 2 kb of genomic DNA. The gene is primarily expressed in neural crest cells.

In humans, mutations in this gene are usually associated with vitiligo, an autoimmune skin condition characterized by progressive patchy depigmentation [30]. In a different study

where 310 probands were screened for mutations in *FOXD3*, in addition to Pax6 and others described in this section, four mutations in conserved regions of *FOXD3* segregated with aniridia or Peters' anomaly (Table 1) [28]. These mutations are p.Thr16Met (heterozygous), p.Pro120Leu, p.Asn173His, and p.Arg273_Gly276dup, where the p.Asn173His mutation disrupts the highly conserved helix 2 of the DNA-binding domain.

TRIM44

This gene translates a tripartite motif-containing protein family member thought to function as a ubiquitin E3 ligase, where ubiquitination can result in either degradation or change the activity of target proteins. In humans it is located on chromosome 11p13, downstream of the loci for *PAX6*, and is encoded by 5 exons spanning 155 kb genomic DNA. Little is known about its normal expression pattern.

A recent study revealed four heterozygous missense mutations in all seven affected individuals of a four generation Chinese pedigree with aniridia [31]. Two of the mutations were in *PAX6*, but were found not to affect its regulation. Two of the mutations were in *PAX6*, but were found not to affect its regulation. The two mutations in *TRIM44* were shown to suppress endogenous *PAX6* expression when transfected into human lens epithelial cells due to overexpression of *TRIM44* protein product, which the authors speculated mediates degradation of *PAX6* through recruitment of other TRIM E3 ligases, resulting in an aniridia phenotype.

Clinical manifestations and management

Aniridia can be categorized into two groups: classic aniridia, which is associated with mutations in *PAX6* [32], and aniridia-like, which is associated with mutations in genes other than *PAX6* [33].

Classic aniridia

Ocular findings for this condition include partial or near total absence of iris, cataract, aniridia-associated keratopathy (ARK), glaucoma, foveal hypoplasia, optic disk hypoplasia and nystagmus making it truly panocular (Table 2).

ARK

The cornea is clear at birth but invariably has a degree of peripheral pannus (Figure 2) that stains with fluorescein. Over the next two decades these patients develop keratopathy [34, 35], which is not surprising as the *PAX6* gene is responsible for embryonic and postnatal development of the cornea (Figure 1). A prior study showed defective cell adhesions, altered cell-to-cell junctions, and wider intercellular spaces due to defective desmosomes in the corneal epithelium [36].

An in vivo study of the central cornea with a confocal microscopy revealed that the morphology of the epithelium varies according to the severity of the disease. In most advanced cases, goblet cells were present together with total loss of corneal epithelium, while milder cases showed an intact epithelium [37]. At the early stage of keratopathy,

studies have shown an increased central corneal thickness, focal opacities at the level of the basal epithelium, and decreased sensitivity of the cornea [38]. Absence of the limbal stem cell niche and conjunctivalisation of the limbal region leads to limbal stem cell deficiency (LSCD) that clearly has a role in ARK. Meibomian gland dysfunction in form of stenosed or atrophic glands was also seen, which leads to defective lipid layer formation resulting in evaporative dry eye that exacerbates the demise of the ocular surface [39].

Clinically, patients present in early adulthood with symptoms of blurry vision, redness, dry eye, and over the years with gradual opacification of the cornea from the periphery to the center [40]. These changes lead to progressive loss of vision. Keratopathy has been graded on basis of symptoms and signs like photophobia, erosions, and vascular pannus in three stages (Table 3) [41]. Recently, evaluation of the limbal palisades using confocal microscopy has allowed correlation between ARK and palisade integrity [42].

Management of ARK depends on the severity of the presenting symptoms and signs. After having established that evaporative dry eye can exacerbate the unhealthy ocular surface, lubricants and anti-inflammatory drops may delay the progression of ARK. In mild to moderate cases of ARK, autologous serum facilitated in maintaining tear film stability and decreasing the frequency of corneal erosion [43]. However, as the disease progresses most patients require surgical interventions. Penetrating keratoplasty (PK) has not been very successful, because of high rate of opacification of the graft [44]. Since LSTD is the main cause of keratopathy, kerato-limbal allograft (KLAL) has shown success in maintaining a stable ocular surface for at least a year [44]. Secondary PK or keratoprosthesis on these eyes that have undergone KLAL, with continuation of the ocular and systemic immunosuppression, demonstrated better outcomes, but long-term stability and maintenance of the corneal clarity was inconsistent [44]. Another study reported a 5-year follow-up in cases of aniridia. The interesting finding in this cohort was that they had subtle iris defects, minimal foveal hypoplasia, and absence of nystagmus. This aniridia variant showed good success with KLAL alone; however, no palisade evaluation was undertaken [45]. Since the ocular surface in advanced cases of ARK is very poor, there is a corresponding increase in rate of rejection of any transplant procedures. A study done on ocular surface stem cell transplantation (OSST) looked at the causes of rejection; 158 patients had undergone OSST with mean follow-up of five years and mean age of 41.7yrs [46]. Aniridia was present in 46% of the patients and the commonest procedure performed was KLAL (80%). All the patients were administered topical and systemic immunosuppressive therapy. Rejection occurred in 31.1% of the patients and the mean time to rejection was 19.3 months. They observed that the etiology did not play a major role in rejection; the important factors for rejection were young age and noncompliance with systemic immunosuppression. These patients needed regular follow-up examinations, as future rejections could not be ruled out.

In recent years, keratoprosthesis has been performed as a primary procedure in cases where there is low probability of transplant success. Outcomes were studied in 26 eyes with aniridia that underwent type one Boston keratoprosthesis, of which 19 eyes had this as the primary procedure for corneal pathology [47]. The mean age was 56 yrs (SD; 11yrs), and the mean follow-up time was 28.7 months. The common complication that occurred in these eyes was the emergence of a retro-prosthetic membrane, where nine of them required

neodymium-doped-yttrium aluminum garnet (Nd:YAG) laser membranotomy. They observed visual acuity (>20/200) was maintained in the primary procedure group better than the secondary group. They also had 77% (20/26 eyes) retention rate, while 6 eyes needed replacement of the keratoprosthesis. Glaucoma was diagnosed in 21 eyes before keratoprosthesis surgery and 5 eyes had undergone glaucoma surgery. Post-keratoprosthesis, 23 eyes were diagnosed with glaucoma. Three of them underwent implant surgery. Four eyes developed phthisis due to severe hypotony, choroidal detachment, retinal detachment, and unspecified infection. Similar complications have been reported previously [48]. Eyes that underwent multiple intraocular surgeries developed a progressive fibrosis in the form of a membrane called anterior fibrosis syndrome [49]. The fibrous membrane grew from the rudimentary iris stump and extended anteriorly, thereby pushing the intraocular lens implants forward. This, in turn, caused endothelial touch and posteriorly extended to cover the ciliary body leading to hypotony. Histopathologically, this membrane showed a mixture of hypo cellular fibrous tissue, consisting of immature collagen fibers with mature collagen fibers with absence of glial tissue, corneal epithelium and endothelium and lens tissue. All the eyes in this study had undergone cataract extraction with iris diaphragm implants, except for one case that had an acrylic sulcus implant. All of the eyes had additional corneal or glaucoma procedures, with an average of total three intraocular surgeries. Close and long-term monitoring of patients with aniridia who have undergone ocular surgeries is necessary to detect rejections or complications.

Glaucoma

Glaucoma in aniridia occurs in early adulthood, but may also occur in infants and toddlers [50]. The incidence ranges from 6% to 75% [1]. The angle in subjects with aniridia was studied by performing serial gonioscopies over a span of 18 years, where it was observed that all cases always had an iris stump [3]. The trabecular meshwork and ciliary processes were visible posterior to the stump. It was noted that patients who developed glaucoma had irregular strands arising from the iris stroma and attaching it to the angle wall. These attachments became thicker and moved forward, causing obscuration of the trabecular meshwork, scleral spur and the ciliary body. Consequently, the iris stump tilted and the angle gradually closed. A study of the angle using an ultrasound biomicroscope showed that along with iris hypoplasia, the ciliary body was also hypoplastic [51]. There was anterior inclination of the ciliary body and an anteriorly placed lens. Initial management is usually with medical therapy, as most of them require surgery at a later stage.

Prophylactic goniosurgery in aniridic patients has been reported [52], with an 89% success rate without topical drops [53]. The mean follow-up in the last report was 9.5 yrs. Trabeculotomy as an initial procedure has been advocated for patients with high intraocular pressure (IOP) [54], with a 83% success rate in patients who underwent the surgery as the initial procedure. The average age in this study was 4.5yrs and the follow-up was 11.6yrs. A recent study with Ahmed valve implant as the primary procedure showed good IOP control when assessed at a mean period of 37.4 months post surgery [55]. A different study documented high IOP and greater number of surgical interventions as the cause of poor visual outcome in aniridic glaucoma eyes, with the probability of blindness estimated to be 69.8% at the end of five years [56]. To address the difficulty in treating aniridic glaucoma,

perhaps a future study showing prophylactic goniosurgery performed at an early age and then comparing various other management options to control increases in IOP may aid in a better understanding of the long-term management of glaucoma.

Cataract

Cataracts are seen in 50 to 85 % of aniridic patients [57]. They are detected at infancy, but become visually significant in the first decade or early adulthood. The morphology of the lens opacities seen are anterior polar, posterior polar and subcapsular cataracts (Figure 3) [58, 59].

Cataract surgery in patients with aniridia comes with unique challenges. Preoperative intraocular lens power calculation can be difficult due to the unstable ocular surface, nystagmus and polar cataracts. Incision size and length need careful consideration to avoid causing or exacerbating LSCD in these patients [60]. Study of the lens capsule showed there was 50% reduction in thickness of the capsule in young patients when compared to normal controls [61]. Due to a hypoplastic iris resulting in absence of a sulcus in aniridia, in-the bag implantation is the only option in these cases. If the anterior capsule is unstable, posterior capsule optic capture must be performed. Iris reconstruction in aniridia can be a challenging task. Outcomes of black iris diaphragm lens in congenital aniridia cases have been studied, where it was found that glaucoma was the most common complication in these eyes who required further surgeries for control of IOP [62]. There are a few case reports on the use of iris implant devices, most of them for traumatic aniridia. Further investigation into the long-term use and safety of such devices is necessary.

Retina

The fovea and optic disc show varying degrees of hypoplasia. Most of the studies show the presence of foveal hypoplasia to be as high as 90% in these eyes [63]. Clinically, there is absence of the macular reflex and foveal pit, and presence of abnormal retinal vessels crossing the fovea (Figure 4) [12]. The presence of foveal hypoplasia has been shown by measuring increased thickness of fovea and central macula by Optical Coherence Tomography (OCT) (Figure 5) [64]. A few case reports have shown retinal detachments, exudative retinopathy, and chorioretinal degeneration in these patients [34, 58, 65]. Electroretinogram (ERG) shows a decrease in amplitude of all the waveforms, suggesting abnormality in all retinal layers [66]. Optic nerve hypoplasia is seen in 10 to 30% of these cases [40, 67]. There has been no proven correlation between the optic nerve and foveal hypoplasia, but most cases show nystagmus. Incidence of nystagmus is as high as 90%, where the majority of these eyes show horizontal pendular nystagmus [1, 63]. Vertical nystagmus as a phenotype variant with foveal hypoplasia, presenile cataract and intact irides has been recently described [68].

Other ocular manifestations

Other ocular manifestations are not typical of classic aniridia, and may include blepharoptosis, which has been reported in association with familial cases of classic aniridia [69]. Surgical management of ptosis in this subset of patients needs a careful approach

according to guidelines in a report recently published for ptosis surgery in aniridic patients [70].

Systemic associations with classic aniridia

Patients with *PAX6* mutations may have systemic abnormalities along with aniridia, which may not manifest in infancy. WAGR syndrome may also be present.

WAGR

Children with WAGR present early in life. Classical WAGR in older children can be diagnosed by aniridia and one of following findings: genital anomalies, Wilms' tumor, and intellectual disability [71]. WAGR without aniridia is rare. A study done on the Dutch population has reported that patients with sporadic aniridia had 67 times higher risk of developing Wilms' tumor (confidence interval 8.1–241) when compared to the normal population [72]. Intellectual disability is the most common neurological manifestation. The other neurological abnormalities may be olfactory problems, hypertonia, and corpus callosum agenesis. Genitourinary findings are cryptorchidism, ambiguous genitalia, and streak ovaries [71]. Obesity has also been observed in most of these patients [50, 71]. Therefore, when an infant presents with sporadic aniridia and genitourinary abnormalities, a molecular diagnosis must be made to exclude the deletion encompassing the *WT1* gene, so appropriate risk management can be put in place for management of potential of Wilms' tumor.

Clinical correlations with *PAX6* mutation types in classic aniridia:

When analyzing the *PAX6* mutation database (http://lsdb.hgu.mrc.ac.uk/home.php?select_db=PAX6), categorizing a type of mutation to a particular phenotype cannot be easily made. For example, when considering missense type of mutations in *PAX6*, a p.Ser43Pro missense mutation leads to total aniridia, a p.Ser121Pro missense causes partial aniridia, and a recently reported p.Pro76Arg missense mutation leads to intact irides. Though some reports have shown certain phenotype frequencies with a particular type of mutation [58], no definitive conclusion can be derived until further functional studies on the protein have been conducted. An exception to this is in the cases of PTC and 3'-UTR type of mutations, where the majority of occurrences lead to total aniridia.

***Pax6* unrelated aniridia**

There are differences in phenotypes between classic aniridia and aniridia-like associated with other etiologies (Table 4). The latter occurs in 10% of cases [73]. Therefore, if an infant presents with an absence of iris, the differences in the clinical features associated with each of the etiologies would help distinguish between classic aniridia from *PAX6* mutations to the other types of aniridia-like from other etiologies. Aniridia has been previously reported in association with other conditions as described below.

Gillespie syndrome

Children present with partial aniridia, cerebellar ataxia, and psychomotor delay. It has been reported to have an autosomal-recessive inheritance, though no gene has been consistently

identified for reported cases of the disorder. Ocular findings show some amount of iris present with absent pupillary zone and there have been reports of presence of a persistent pupillary membrane along with the above findings, diagnosis of the syndrome remains clinical [74]. Complete absence of iris has been reported with Brachmann-de Lange syndrome and Omenn syndrome [75, 76].

Duane's syndrome, megalocornea are other reported associations with aniridia. These have been single case reports without detail genetic screening [77, 78].

Future

Apart from the genes listed in the etiology section, a putative causal gene that can be added to this list is *Notch1* [79]. This gene encodes the Notch1 receptor as part of the Notch pathway, and in humans resides on chromosome 9q34.3. The Notch pathway is a highly conserved signaling cascade involved in numerous differentiation processes during embryonic and postnatal development, in addition to maintenance of adult organs capable of self-renewing. It has been shown to be required for melanocyte development, and therefore pigment formation in the skin.

A recent report investigating the development of the anterior pigmented epithelium of the ciliary body indicated that the Notch pathway could play a role in iris development [79]. The notable findings were that loss of canonical Notch signaling, through Notch 2 or RBJ absence, results in normal iris development and absence of the ciliary body, while Notch1 gain-of-function result in aniridia with ciliary body hyperplasia, the latter causing glaucoma-like disease.

Treatment for aniridia has taken a dramatic step forward recently through a study examining aminoglycosides that suppress expression of premature stop codons (PTCs) in *PAX6* and allow transcriptional read-through, therefore producing a functional protein. It has been determined that 72% of all *PAX6*-associated aniridia are caused by missense mutations, such as nonsense, splice-site, and frameshift mutations that result in PTCs [12]. However, some missense mutations cause a change of amino acid and not a PTC. A recent study has developed a postnatal nonsense mutation suppression approach for in-frame PTCs associated with aniridia [80]. In this approach, an aminoglycoside, named ataluren, promotes read-through of PTCs, because during mRNA translation a near-cognate aminoacyl tRNA is inserted into the position of the PTC. A functional *PAX6* protein is therefore produced. This approach was tested on the malformation defects exhibited by the Pax6-deficient mouse model of aniridia. They found that ataluren promotes dose-dependent read-through of all three nonsense codons, with the highest read through at UGA, followed by UAG and then UAA. Read-through efficiencies were influenced by the nature of the nucleotide following the nonsense codon, where a pyrimidine (in particular cytosine, C) would increase efficiency of read-through. They demonstrated that the mammalian eye retains marked developmental plasticity into the postnatal period and molecular remodeling by reversing corneal, lens, and retinal malformation defects and restoring electrical and behavioral responses of the retina.

Expert commentary

Currently, our understanding of the mechanism of aniridia is rudimentary. Increased awareness of total/partial iris defects (total/partial aniridia) needs to be implemented so appropriate genetic testing can be done to find a molecular diagnosis rather than a clinical one. Improved genotype–phenotype correlation will likely allow reclassification of congenital aniridia according to the responsible gene. Mutation detection for PAX6 is 43.3% [81]. Even when other genes that cause aniridia like phenotype are considered, current genetic testing is not capable of finding all gene mutations. At present, treatment of aniridia-related glaucoma maybe hindered by inappropriate diagnosis, for example, while goniotomy is considered for PAX6-related aniridic glaucoma, goniotomy for FOXC1/PITX2-related glaucoma with aniridia would likely fail.

Five-year view

The classification of aniridia is likely to move to a molecular genetic one in the near future given our increased understanding of both causative mutations in different genes and the extraocular association of such mutations.

The role of other genes on 11p13, example *TRIM44*, on *PAX6* expression will also help understand a molecular diagnosis. This will impact accurate genetic counseling and better therapeutic interventions. Specifically for PAX6-related aniridia, advances in stem cell research with early intervention may help delay the process of keratopathy, and a better understanding of iris development may allow therapies for iris growth.

Acknowledgments

Financial and competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Funding

We acknowledge support from NIH CORE Grant P30 EY08098 to the Department of Ophthalmology, from the Eye and Ear Foundation of Pittsburgh, and from an unrestricted grant from Research to Prevent Blindness, New York, NY.

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Key issues

- Two types of aniridia: classic aniridia associated with mutations in PAX6 and aniridia-like associated with mutations in genes other than PAX6, such as FOXC1, PITX2, and CYP1B1.
- Classic aniridia is a panocular disorder with iris hypoplasia, aniridia-associated keratopathy, cataract, foveal and optic nerve hypoplasia and nystagmus. FOXC1 aniridia-like presents usually with dental anomalies, and PITX2 aniridia-like presents with heart and umbilical hernias and CYP1B1 has no systemic manifestations but presents with glaucoma at birth.
- Sporadic cases of aniridia need to be screened for WAGR syndrome and need continuous monitoring for a defined period.
- All types of management in aniridic cases have better outcomes if diagnosed early.
- Most interventions in aniridia management are surgical in nature
- Prolonged monitoring and close compliance need to be adhered for good outcome of management.

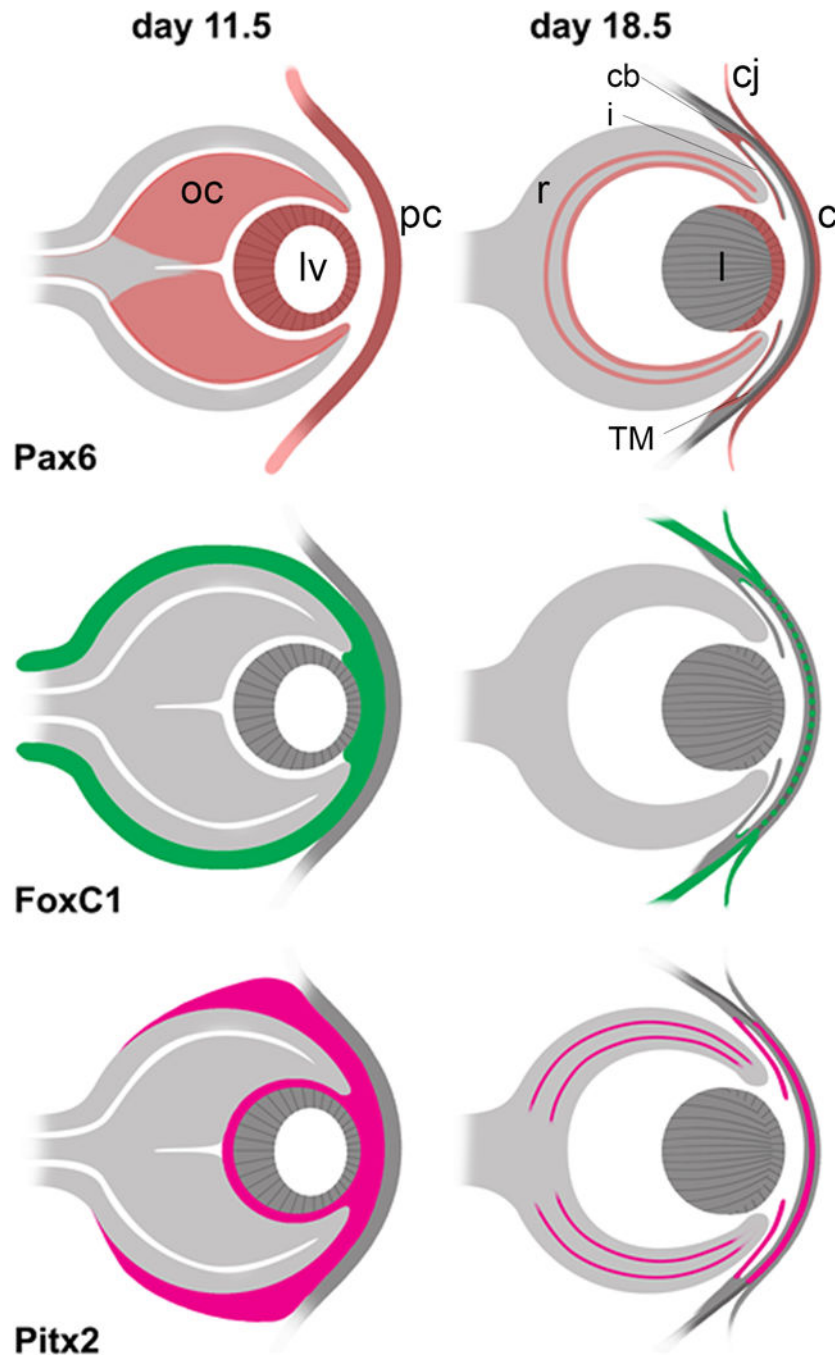


Figure 1. Expression pattern of *Pax6*, *FoxC1* and *Pitx2* in the early and late eye

The expression patterns for *Pax6*, *FoxC1*, and *Pitx2* are presented based on studies in mice and humans [82–87]. Early expression is shown at embryonic day 11.5 (E11.5), which represents day 33 in human development, and late expression is shown at E18.5, which is close to prenatal in humans. For *Pax6*, early expression is seen in the lens vesicle (lv), optic cup (oc), and presumptive cornea (pc) [86]. Expression later in the prenatal is restricted to the ganglion cell layer and inner and outer portions of the inner nuclear layer of the retina (r), where the latter points to expression specifically in the amacrine and horizontal cells

[85]. At this stage, *Pax6* is also expressed in the epithelia of the cornea (c), conjunctiva (cj), lens (l), ciliary body (cb), iris (i) and trabecular meshwork (TM). For both *FoxC1* and *Pitx2*, expression in the early eye is seen in the neural crest cells of the periocular mesenchyme that surrounds the oc, in the intracellular space between the lv and pc, and the intracellular space between the inner oc and lv [84]. In the prenatal eye, *FoxC1* expression is reduced to the conjunctival epithelium, sclera and trabecular meshwork [82] and *Pitx2* expression is reduced to the iris [83], and according to a study of expression in human eyes is expressed in the corneal epithelium, the ciliary body non-pigmented layer and the nuclear layers of the retina [87]. *Pitx2* is present in the corneal stroma but *FoxC1* is much reduced in this layer [82, 83].

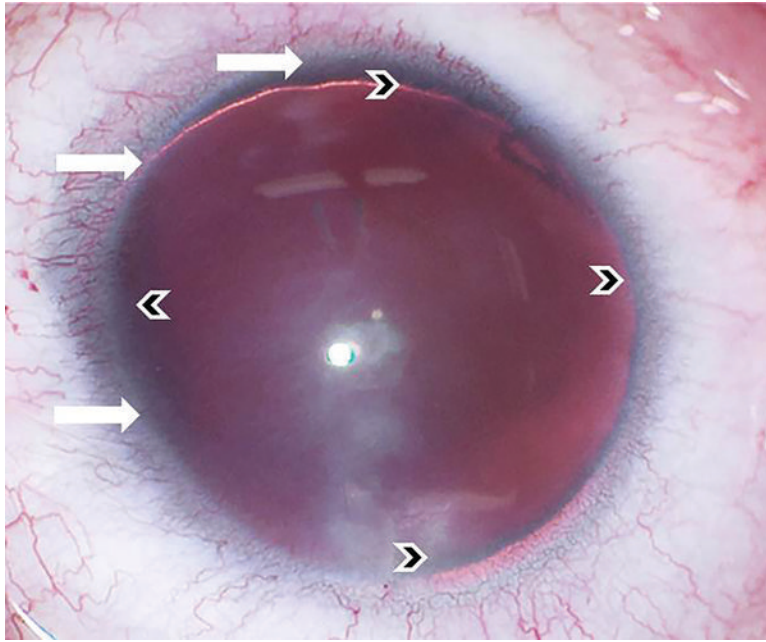


Figure 2. Aniridia showing absence of iris and peripheral pannus

Eye of 20-year-old female showing corneal and limbal changes. Indicated are presence of pannus and absence of a well demarcated limbus (white arrows), in addition to absence of the iris (small black arrows).

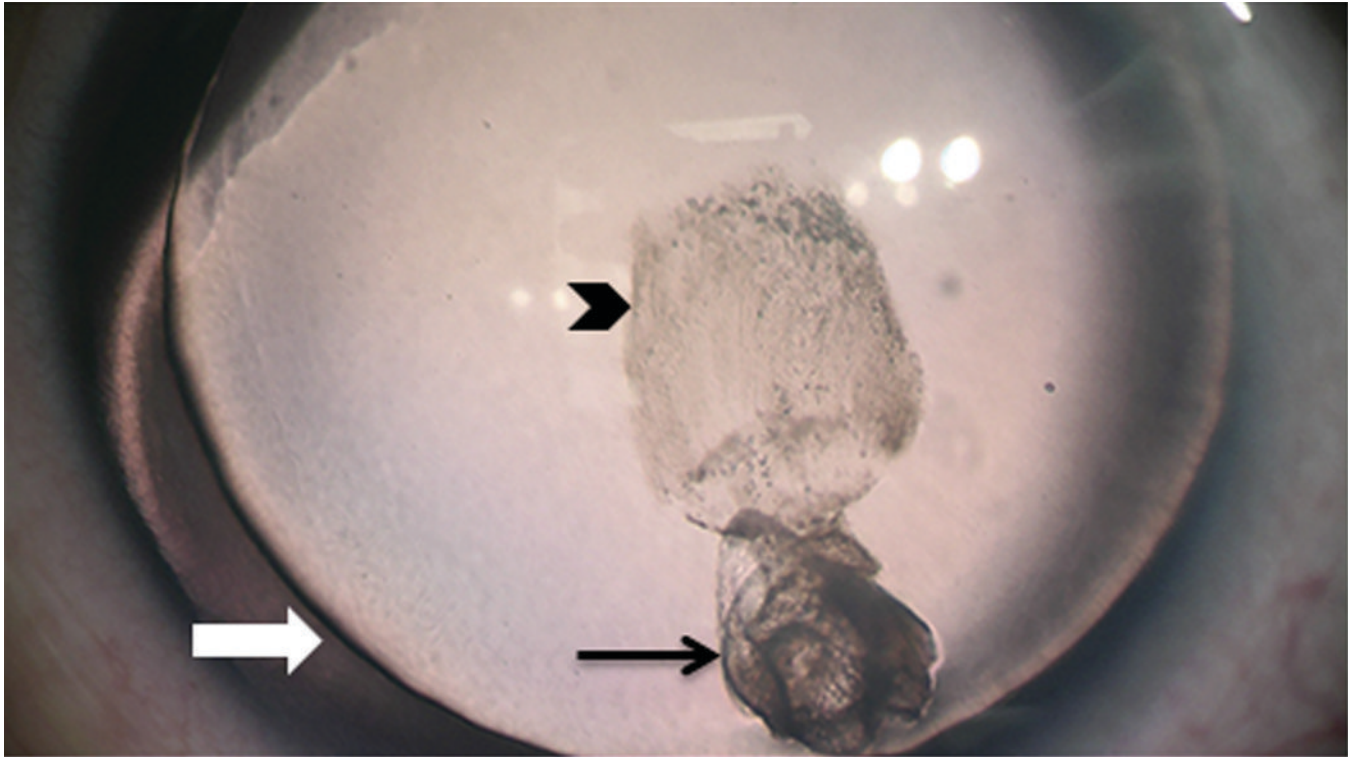


Figure 3. Anterior polar cataract and subcapsular lens opacities

3-year-old male showing lens changes. Subcapsular opacity (small black arrow), anterior polar lens opacity (long black arrow) and absence of the iris (white arrow) are shown.

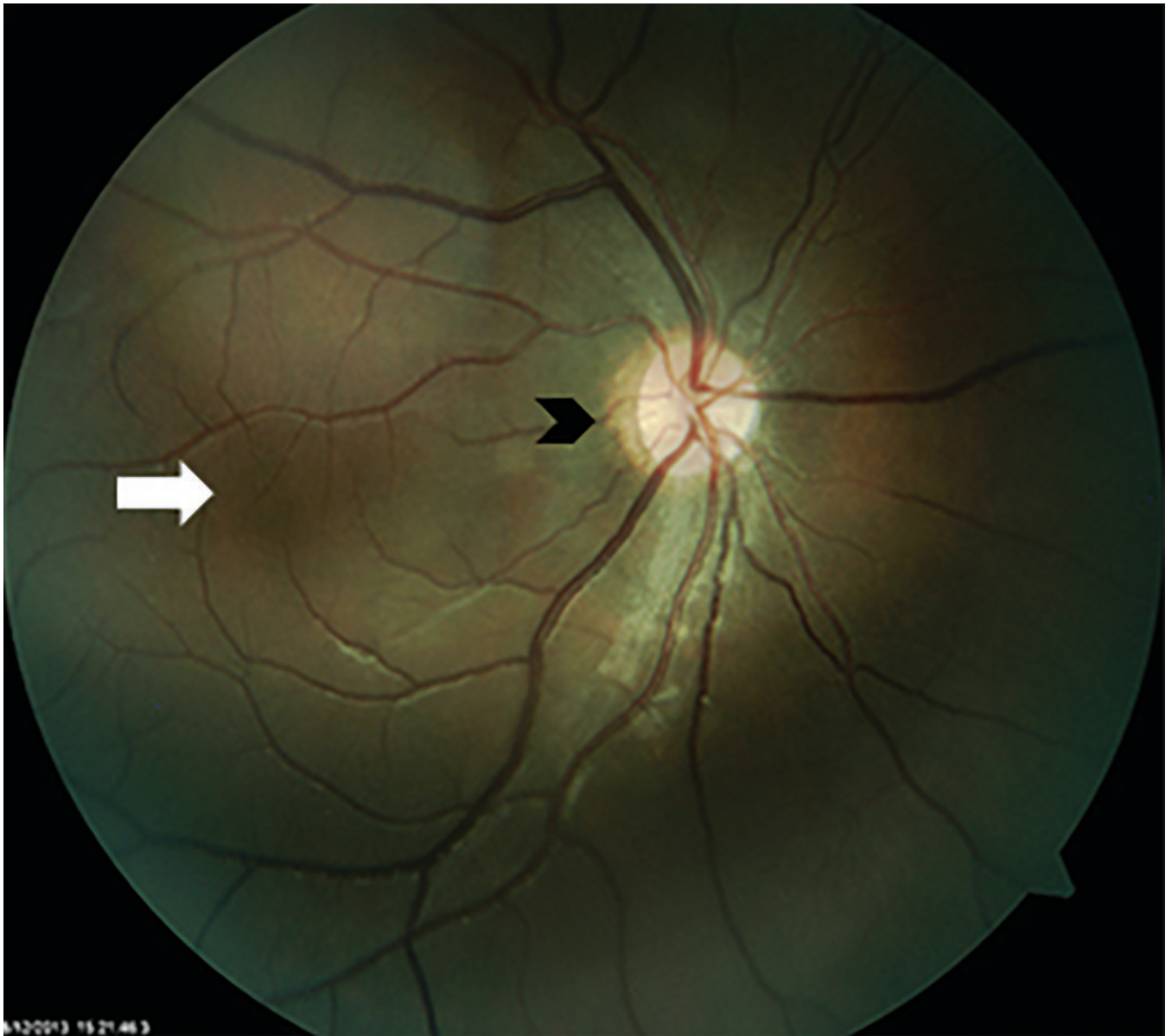


Figure 4. Foveal hypoplasia in aniridia

Fundus photo of a 16-year-old boy. Note the blood vessels crossing the fovea (white arrow) and optic disc hypoplasia (black arrow).

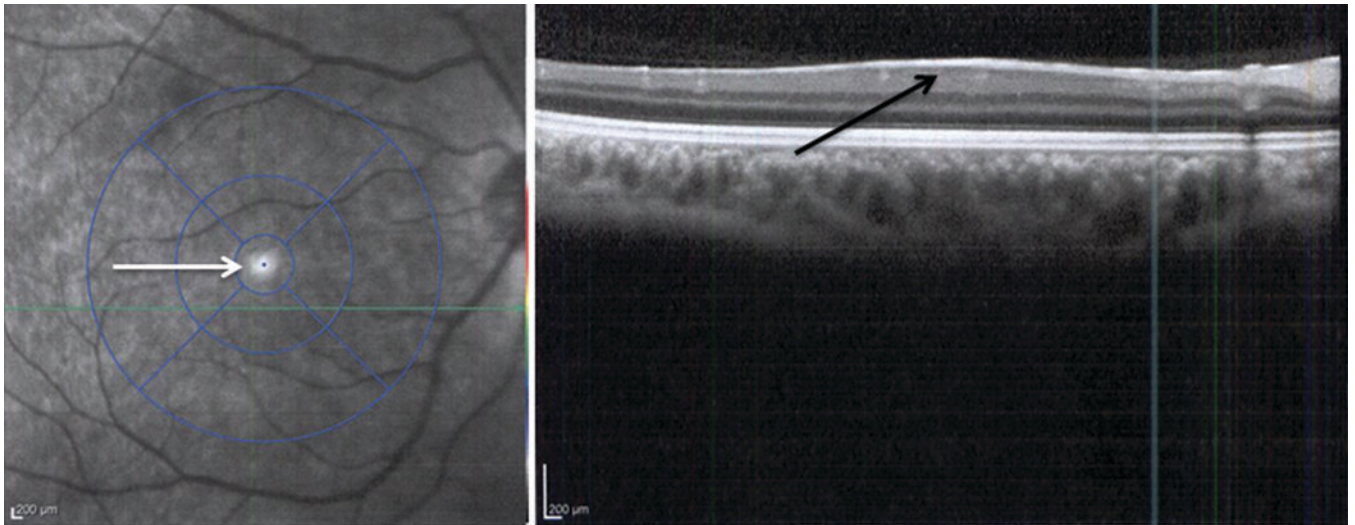


Figure 5. OCT of thickened fovea and absence of pit
OCT images of the same eye (Figure 4) showing absence of a foveal pit and a thickened fovea (black arrow).

Table 1.

Etiology of partial and total aniridia

Phenotype: Partial aniridia	
Etiology:	<i>PAX6</i> [73] [69] <i>FOXC1</i> [88] <i>PITX2</i> [89] <i>CYP1B1</i> [32]
Phenotype: Total aniridia (iris stump on gonioscopy)	
Etiology:	<i>PAX6</i> [81] <i>FOXC1</i> [33] <i>CYP1B1</i> [90] <i>FOXD3</i> [28] <i>TRIM44</i> [31]

* numbered references for *FOXC1* and *CYP1B1* match to case orders in the text

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Table 2.

Features of classic aniridia

Condition	Previous studies [35]	Schanilec et al., 2014 [35]	Chang et al., 2014 [63]	Singh et al., 2014 [91]
Nystagmus	81.8–95%	76%	68%	N/A
Cataract	50–80%	56%	53%	40.3%
Glaucoma	6–75%	64%	20 OH****	36.3%
ARK	20–64%	48%	69%	59.9%
Dry eye	94%	1%	N/A	N/A
FH	10.7–54.5%	20%	91%	87.7%
ONH	10.7–75%	20%	N/A	N/A

ARK: aniridia-associated keratopathy; FH: foveal hypoplasia; ONH: optic nerve hypoplasia; OH: ocular hypertension

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Table 3.

Staging of aniridia-related keratopathy

Stage	Erosion/ulcer	Pannus	Signs & symptoms	Others
1	2 recurring erosions/ulcer in 6 months	<1mm from limbal arch	Slight epiphora and photophobia	Small disorder in absorption of fluorescein
2	> 3 recurring erosions/ulcer in 6 months	peripheral half of the cornea +/- sub epithelial fibrosis	Constant red eye, epiphora, photophobia	Permanent instability of tear film
3	Permanent signs of corneal erosions	Central cornea involved	Constant red eye, epiphora, photophobia and loss of vision	Permanent instability of tear film

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Table 4.

Classic and aniridia-like phenotypes

Aniridic genes	<i>PAX6</i> (C)	<i>FOXC1</i>(AL)	<i>CYP11B1</i> (AL)	<i>PITX2</i> (AL)
Keratopathy	✓	-	-	-
Iris abnormality	✓	✓	✓	✓
Glaucoma at birth	-	-	✓	-
Cataract at birth	-	-	-	-
Foveal hypoplasia	✓	-	-	-
Nystagmus	✓	-	-	-
Optic disc	Hypoplasia	-	Cupping	-
Posterior embryotoxon	-	✓	-	-
Systemic anomalies	Kidney, brain	Facial, dental	-	Cardiac, umbilical hernia

AL: aniridia-like; C: classic aniridia