

# Clinical Findings in a Family with Aniridia due to PAX6 Mutation

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## SUMMARY

**Background:** inborn isolated aniridia is rare bilateral impairment of several eye structures manifesting mainly by absence of iris, photophobia and decreased visual acuity. There are also others ocular symptoms associated with aniridia such as nystagmus, strabismus, eyelid ptosis, amblyopia, serious refractive errors, anisometropia, corneal changes, impairment of the lens, chamber angle dysgenesis, optic nerve and macular hypoplasia and congenital or secondary glaucoma. The most frequent aetiology of this eye dysgenesis is mutation in PAX6. Aim of this report is to describe ocular findings in the family with familial aniridia (MIM #106210), to debate their severity, prognosis and therapy options.

**Material and methods:** assessment of previous medical history and actual ophthalmological findings in 4 persons of 3 generation family with aniridia. According to the compliance, the patients underwent these tests: assessment of the visual acuity, intra-ocular pressure, refraction test, slit-lamp examination and biomicroscopy, pachymetry test and OCT examination. The genetic counselling was performed with subsequent PAX6 mutation analysis.

**Results:** all of the examined aniridia family members showed severe symptoms of the disease, the aniridia and photophobia were present. Positive age related correlation showed progressive visual acuity decrease to the practical blindness due to aniridia-associated keratopathy, secondary glaucoma and cataract. DNA analysis revealed presence of p.Gln180X PAX6 mutation in all of the affected persons. The mutation leads to shortened and therefore non-functional protein.

**Conclusions:** PAX6 mutations leading to premature termination of protein translation are frequently associated with severe symptoms of aniridia and small intrafamilial variability of ocular impairment. This fact is also well demonstrated in members of family described by this report, the symptoms are severe and progressing with age. Therapy is difficult and often with partial success, such in case of secondary glaucoma in young girl from this family. Any eye surgery must be individually judged due to risk of several post-operative complications. And more, the poor vision in aniridia patients is progressively worsening in time to practical blindness.

**Key words:** aniridia, PAX6, macular hypoplasia, glaucoma

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## INTRODUCTION

Isolated congenital aniridia is a rare pathology, the estimated incidence is approximately 1/65000 – 1/96000 (11). Two thirds of cases of aniridia occur familiarly, one third occur sporadically (19). Isolated congenital aniridia represents a panocular anomaly with bilateral occurrence, in which complete or partial absence of the iris and further anomalies predominate as a consequence of defective development of the chamber angle, cornea, lens, retina and optic nerve. Patients have reduced vision, photophobia, with frequent occurrence also of nystagmus and strabismus (25). Aniridia is the result of abnormal in-

teraction of the neuroectoderm in the region of the prosencephalon and adjacent ectoderm, as a consequence of mutations in PAX6. The protein PAX6 belongs to the family of transcriptional regulators, and has an important role in the development of the eye, but may also influence the development of the brain and pancreas. Its expression takes place in the neuroectoderm of the prosencephalon at the time of induction of the optic disc. After its division into two parts, with the formation of ocular capsules, the expression of PAX6 is restricted to the anterior edge of these capsules. PAX6 then indicates the formation of a placoid lens in the ectoderm adjacent to the ocular capsule. The continuing expression of PAX6 acting together with other tran-

scription factors has an important role also in the development of the lens (29). The expression of PAX6 is also present in the cornea, the conjunctiva, ciliary epithelium and retina, and continues also postnatally (20).

Isolated aniridia as a consequence of the affliction of PAX6 shows autosomally dominant heredity, the risk of incidence of this pathology for descendants of an affected person is theoretically 50%. PAX6 is located on chromosome no. 11, within the region of 11p13. Various types of mutations may occur in this gene, as a consequence of which a formation of a shorter protein or a protein with a different sequence of amino acids takes place. These lead to an impairment of the function or formation of the PAX6 pro-

tein (7). The defective product of the gene leads to an impairment of the morphogenesis especially of the iris. People with congenital aniridia have only one functional PAX6 allele, the second allele is (partially or completely) disabled in its function by the mutation – this therefore concerns a heterozygote constitution. On the basis of case reports describing families in which aniridia was present in both parents, it is assumed that the presence of 2 mutations in PAX6 (homozygote, compound heterozygote) is not viable (12). Penetration of the pathology is full, expression however is variable, and the consequence of this is variable clinical manifestations, sometimes even within the same family. Aniridia (total or partial) occurs in patients, in addition to further connected ocular symptoms, or only other affiliated ocular abnormalities. We differentiate total aniridia from partial aniridia. Even if minimally, the rudiments of iris tissue are gonioscopically mostly perceptible even in the case of total aniridia.

In the case of total aniridia, a wide pupil is formed, reaching all the way to the edge of the cornea, as a result of which the entire equator of the lens is visible, as is sometimes also the suspension apparatus with the ciliary projections. Pathologically-anatomically we mostly find rudimentary tissue of the iris, missing muscles, the pigment epithelium is ectopic and the ciliary projections are generally shorter (21, 25).

The incidence of glaucoma in the case of aniridia is approximately 6-75%. It usually appears at pre-adolescent or early adolescent age (19). Glaucoma develops as a consequence of abnormalities in the drainage pathways of the chamber angle, which prevent the drainage of the chamber fluid via the Schlemm's canal. Margo et al. (15) described abnormalities of the irido-corneal angle in patients with aniridia who also had presence of glaucoma, in which the peripheral residues of the iris in the majority of these patients overlapped the trabecular meshwork. In the case of congenital glaucoma, the drainage pathways are obturated by a membrane containing capillaries originating from the rudiments of the iris. In secondary glaucoma the drainage pathways are blocked by the residual iris tissue. The Schlemm's canal may be missing in both types of glaucomas (4, 8, 25).

In patients with aniridia, the cornea measures 100 µm more than the average thickness of the cornea (3). A

typical manifestation is the presence of secondary corneal changes at an early age (the first changes appear in the first decade of life). PAX6 mutation results in changes in the corneal expression of cytokeratin, cellular adhesion and the expression of glycoconjugate. This, together with a deficit of limbal stem cells, contributes to the fragility of the cornea and to aniridia associated keratopathy (AAK). The incidence of keratopathy is stated at approximately 20% (4, 27). In aniridia the production of tears is normal, but tears lack normal viscosity and easier rupture of the lacrimal film occurs. The protective value of the lacrimal meniscus is reduced, thus opening a pathway for irritation processes on the surface of the eye (4, 11, 14, 25).

There are sometimes residues of the vascular tunic on the lens (tunica vasculosa lentis), as well as a persistent pupillary membrane and isolated coloboma of the lens, and ectopia of the lens, subluxation and dislocation of the lens occurs in a low percentage of cases. Present opacities in the lens may occur congenitally. Cataracts develop in more than one half of patients (50-85%) (19). This may typically begin in childhood or afflict young adults. The impaired function of the retina may be contributed to by its defective development during embryogene-

sis and subsequently during life by a phototoxic effect. A typical manifestation is hypoplasia of the macula, which is histologically characterised by a substitution of the structure of the fovea by a continuous layer of ganglion cells. Foveal hypoplasia is manifested in reduced foveal reflex, macular hyperpigmentation, abnormal vascular remodelling and reduction of the avascular zone. OCT findings identify central foveal thickening and a smaller macular volume, and the foveal depression is generally not preserved (11, 13, 17, 22, 26, 31).

Nystagmus is not a universal finding, but occurs in approximately 85-92% of patients with aniridia. The cause of its occurrence is the hypoplasia of the macula itself, with congenitally caused reduction in vision (25).

## MATERIAL AND METHOD

4 persons from one family were examined with the incidence of aniridia in three generations (fig. 1). This concerned the following persons: brother and sister, their mother and the mother's father. The phenotype of the pathology is severely expressed in this family. These persons underwent ophthalmological and genetic examinations. Within the framework of the genetic examination, the family was provided

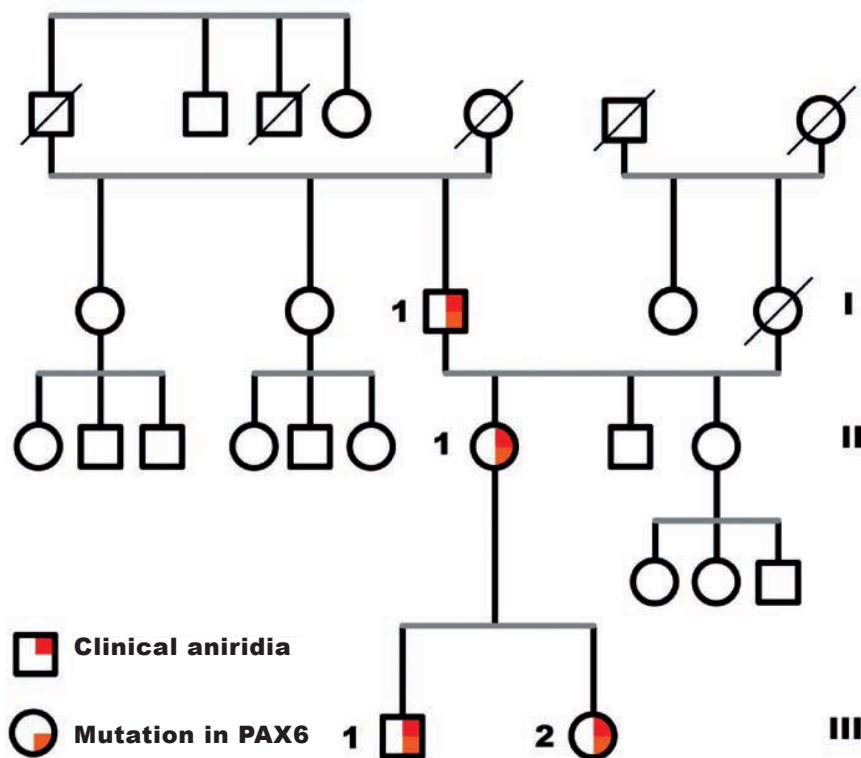


Fig. 1 Genealogy of family with isolated congenital aniridia and PAX6 mutation.

with a genetic consultation, and subsequently also a DNA analysis on the basis of informed consent – an analysis of the presence of mutation in PAX6 with the help of direct sequencing.

The usual examination procedure was used in the examination by the ophthalmologist. First of all visual acuity was determined without correction, then with correction, and measurement of refraction was performed using an auto refractometer. Subsequently measurement of intraocular tension was conducted on the patients using a slit lamp. Pachymetry was conducted on the younger female patient with congenital aniridia. It was possible to obtain photo documentation of the fundus for both the youngest patients with a transparent cornea. Examination by OCT succeeded with difficulties only in the youngest female patient (sister), within the framework of an attempt to examine the papillas of the optic nerve and the macula.

## RESULTS

DNA analysis detected the presence of a mutation c. 538C>T/p.Gln180X in PAX6, located in exon no. 8. This mutation was found in all 4 persons with the incidence of congenital aniridia. Extraocular affliction of the individuals in this family was not anamnestically recorded.

The seventy five year old man (patient I-1, fig. 1) is continuously medicated for congenital total aniridia, slight horizontal nystagmus, secondary glaucoma and fully developed AAK with vascular leukoma (fig. 2). Upon examination by slit lamp it is possible only to guess at rudiments of iris tissue due to the non-transparent cornea. According to the anamnesis and documentation, the patient is aphakic. Vision in the right eye with aphakic correction and without correction is 0.5 m fingers in the right eye, in the left eye the patient is blind. It was not possible to assess further symptomatology in the patient either objectively or according to the documentation.

Significant convergent strabismus is present in the thirty five year old mother (patient II-1, fig. 1) with congenital bilateral aniridia with photophobia, and also with horizontal nystagmus and a higher degree of AAK (fig. 3). The cornea has had reduced transparency and vascularisation for several years, and as such does not enable examination of the intraocular structure

and the ocular fundus. Visual acuity in the right and left eye is stable at 0.03 and 0.02. It was not possible to measure refraction and noncontact tonometry. Intraocular tension according to Schiötz was 3.5 / 5.5 and 3.5 / 5.5. According to the older documentation and according to the patient's own glasses correction, a myopic refractive error was determined in the patient (-3.75dsf. bilaterally, no data about refraction was found in the older available documentation). According to the documentation, incipient turbidity of the lens appeared in the patient at the age of sixteen, at the age of seventeen local antiglaucomatous therapy was commenced with beta blockers for secondary glaucoma. The last mention of the ocular fundus is in the older documentation from 1998 (when the patient was twenty years old), when a white disc of the optic nerve was found. Further evaluation of the ocular fundus was not possible at this time.

The eight year old boy (patient III-1, fig. 1) had a diagnosis of congenital total bilateral aniridia with photophobia immediately after birth. The presence of severe myopia with myopic astigmatism (refraction of right eye -5.25 D sf. - 1.75 D cyl. ax. 22°, refraction of left eye -7.0 D sf. -2.0 D cyl. ax. 173°) was determined also in this patient, as well as objectively slight convergent strabismus. Visual acuity with correction is bilaterally 0.15. Upon examination by slit lamp, the absence of an iris was determined, and a fine vascular sketch was present on the cornea perilibally, 1 capillary in the right eye permeated through the limbus in the direction toward the centre (fig. 4). Using the slit lamp, isolated opacities were also found in the lens of the right eye, a zonular cataract was indicated in the left eye. Papilla with central minor excavation is present on the ocular fundus bilaterally – without perceptible glaucoma changes, a deficiency of a foveal reflex and thinning of the pigment epithelium of the retina (RPE) mainly in the periphery (fig. 6). Ocular tension is stable – around 15 Torrs (it was not possible to perform gonioscopy, OCT, pachymetry due to poor co-operation and concentration together with poor fixation).

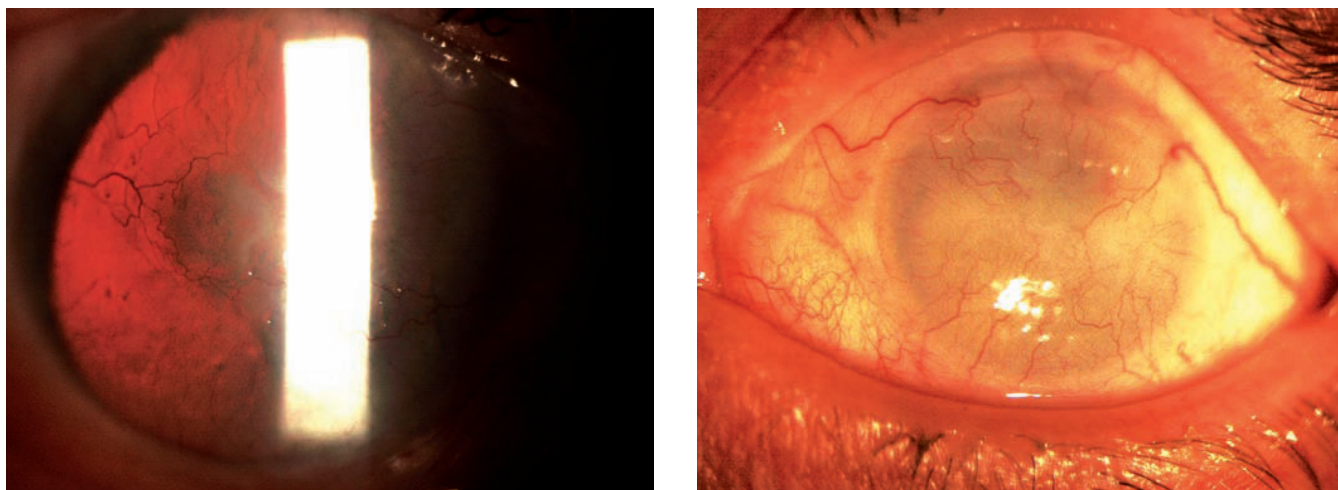
The seven year old girl (patient III-2, fig. 1) was born from the mother's 2nd physiological pregnancy, birth within the term per S.C. from the ocular indication of the mother. An ocular defect was determined immediately

after birth and during infant age the patient was examined under general anaesthesia. At the time of measurement total bilateral congenital aniridia was present, with photophobia, refractive error (myopia gravis with myopic astigmatism) and incipient posterior polar cataract more in the right eye (fig. 5). Vision in the right eye was 0.1 bilaterally with and without correction, refractive error in right eye: -7.25 D sf. - 1.5 D cyl. ax. 52° and in left eye: -9.0 D sf. -2.0 D cyl. ax. 125°. Examination by slit lamp demonstrates incipient perilimbal greying on the cornea and mild vascularisation of the periphery of the cornea within the framework of AAK.

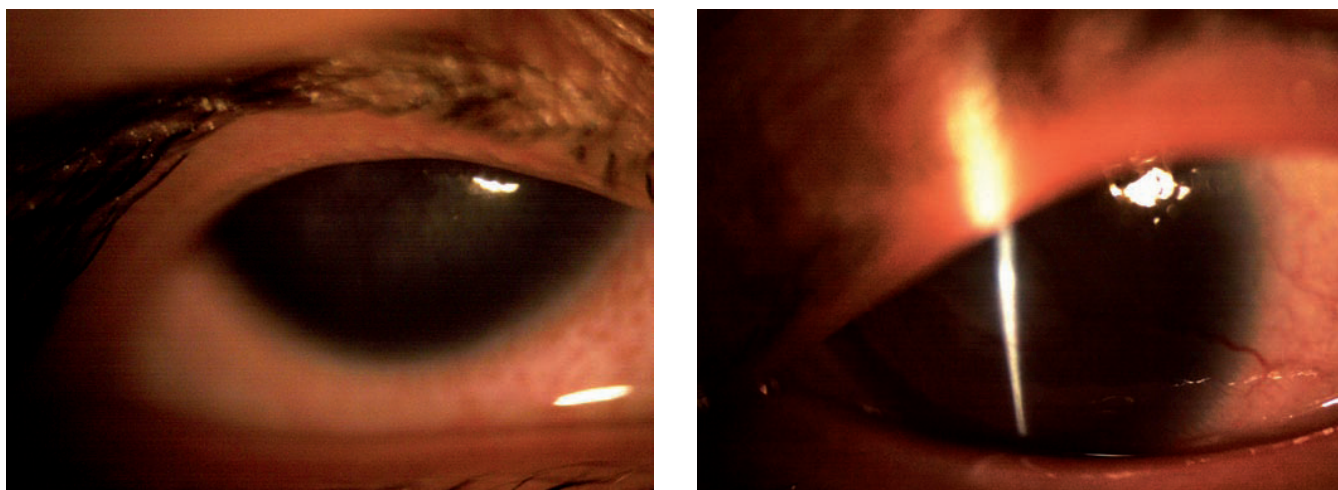
According to the documentation, at the age of six years secondary glaucoma was diagnosed in the patient and local monotherapy with beta blockers was commenced. Due to unsatisfactory intraocular tension, a fixed dual combination was selected after six months (brinzolamide with timolol). With regard to the thickness of the patient's corneas (678-680 µm according to pachymetry), intraocular tension is within the range of 20-25 torrs. OCT scans of the papillas, obtained with difficulty (poor fixation of patient), detected smaller papillas (1.23 mm<sup>2</sup> in right eye and 1.17 mm<sup>2</sup> in left eye), values of the neuroretinal rim and cup/disc ratio testify to advanced glaucoma changes with reduced RNFL. With regard to poor fixation and the quality of the scans, the validity of the examination itself was poorer. According to the OCT scans of the macula, foveal thickening was determined at 279 µm in the right eye and 233 µm in the left eye, macular volume 6.56 mm<sup>3</sup> in the right eye and 11.08 mm<sup>3</sup> in the left eye. Upon biomicroscopic examination there is a bilateral finding of excavation 0.8-0.9 with residual neuroretinal rim especially in the left eye, the macula is without foveal reflex and the retina is thinned mainly in the periphery with showing sketch of choroid (fig. 7, see photo of fundus). Gonioscopic examination was not performed due to photophobia and difficult co-operation.

## DISCUSSION

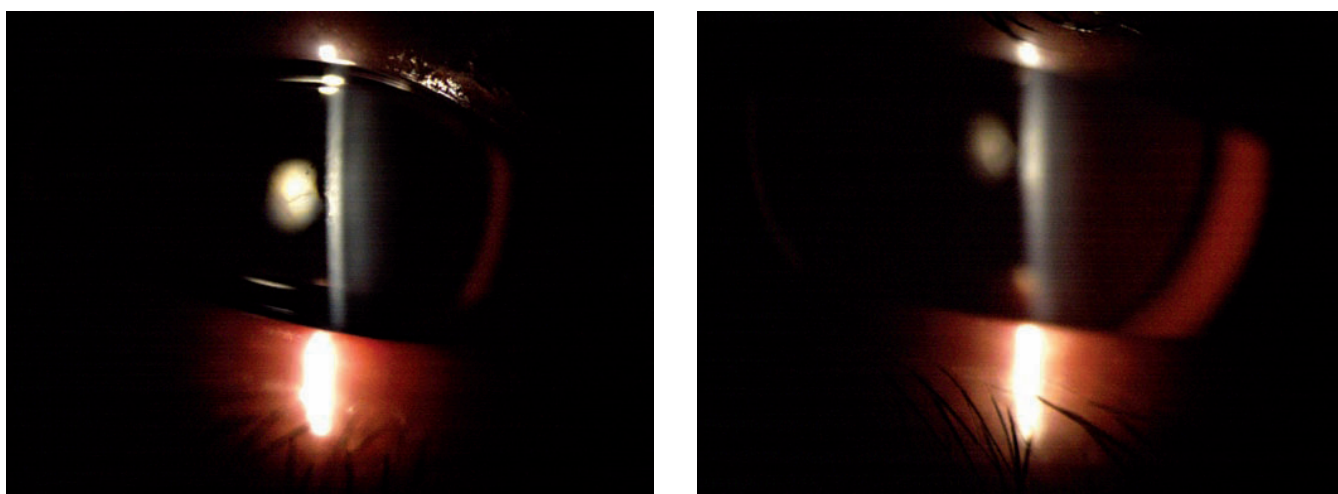
Mutations in PAX6 are responsible for the incidence of isolated aniridia, in isolated cases this may concern a mutation in the ultra-conserved region of the gene ELP4, 150 kb distally from PAX6 (2). At present over 286 PAX6 mutations are known, in which



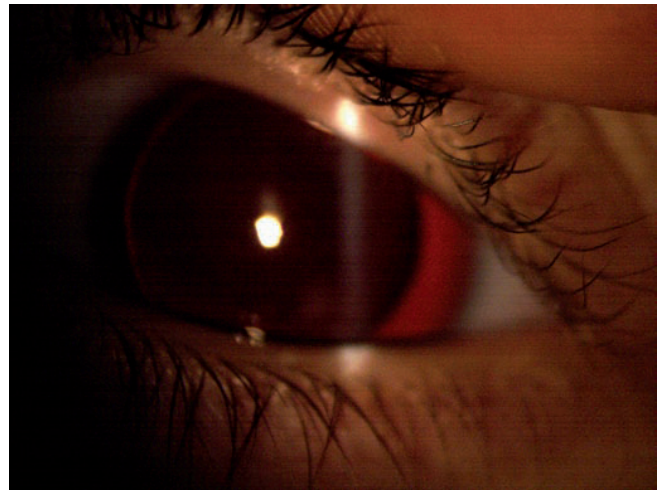
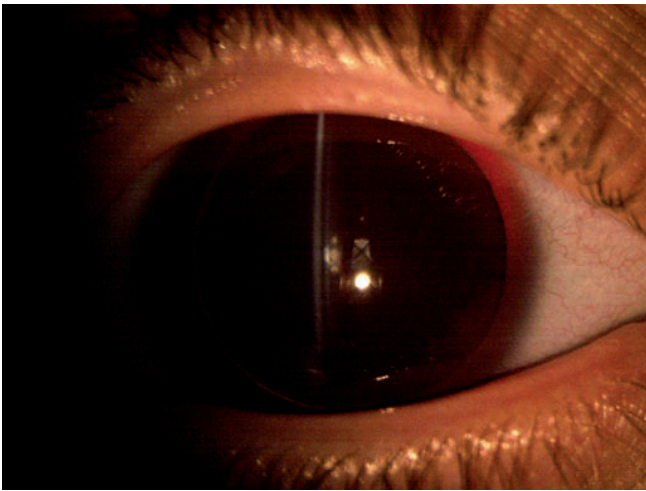
**Fig. 2** Patient I-1: right eye (A) and left (B), aniridia, high degree of AAK.



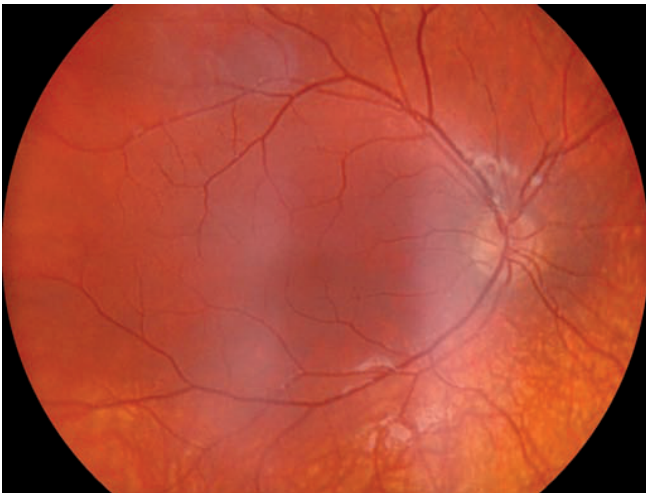
**Fig. 3** Patient II-1: right eye (A) and left eye (B), aniridia, higher degree of AAK.



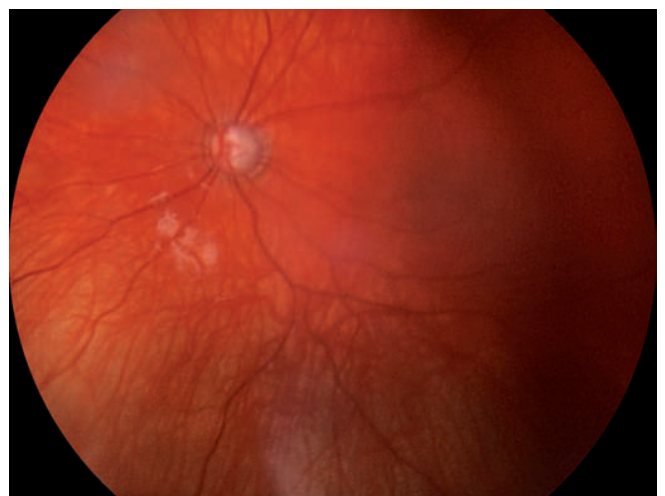
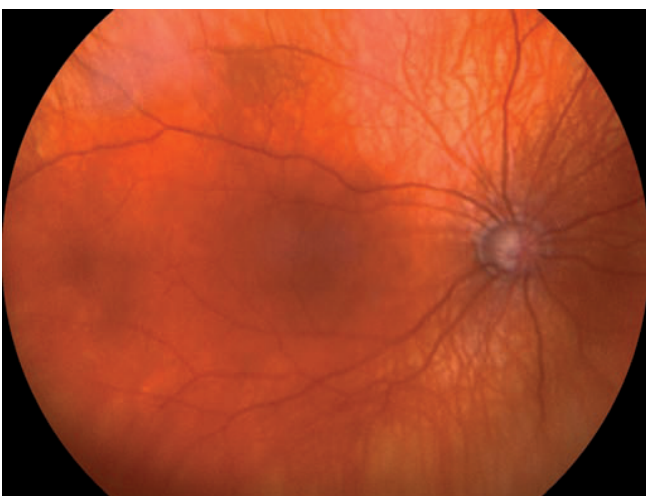
**Fig. 4** Patient III-1: right eye (A) and left eye (B), aniridia, visible equator of lens, minimal corneal changes.



**Fig. 5** Patient III-2: right eye (A) and left eye (B), identified aniridia, visible equator of lens, minimal corneal changes, identified cataract in right eye



**Fig. 6** Ocular fundus in patient III-1: right eye (A) and left eye (B); perceptible thinning of RPE (retinal pigment epithelium) in periphery.



**Fig. 7** Ocular fundus in patient III-2: right eye (A) and left eye (B), glaucoma changes of papilla n.II, thinning of RPE.

approx. 90% of these were linked to the incidence of isolated aniridia or connected phenotypes. Mutations may occur within the scope of the entire PAX6, the most frequently occurring are "non-sense" mutations, as a consequence of which premature termination of protein formation takes place. More than one half of these non-sense mutations occur in exons 8-11. In total almost 90% of PAX6 mutations leading to isolated aniridia are of the character of non-sense or alter the sensory framework (28).

Non-sense mutations are very often the cause of severe affliction with lower variability of the phenotype. In this family mutation c.538C>T was found in exon no. 8, as a result of which glycine in position 180 is recorded as a Stop codon, therefore protein formation is terminated immediately. This mutation has been described only once previously in a family with the incidence of aniridia (16). In the family we describe, this is linked to a severe phenotype impact, with imperceptible variability of symptoms, in accordance with the character of non-sense mutations in PAX6. In many families with aniridia, visual acuity is less than 20/60 (0.33) and lower than 20/200 (0.1) in more than 60% of cases within the framework of congenital foveal hypoplasia or secondary glaucoma (25). The refractive errors found in aniridia include myopia, hypermetropia, astigmatism, and frequently also anisometropia. Haploinsufficiency as a consequence of heterozygote mutation of PAX6 is frequently linked to a high refractive error, especially short-sightedness (10). In the members of this family with total aniridia described in this study, visual acuity is within the range from blindness to best vision with correction of 0.2. There is a prognosis of deterioration of visual acuity especially in patients from families with severely expressed symptomatology (phenotype expression) of the pathology. Keratopathy associated with aniridia is identified in the individual stages of the pathology according to the age of patients in all of the persons we examined with aniridia. In this family, AAK occurs at an earlier age, and the course of the pathology with progressive deterioration of vision takes place more rapidly.

OCT of the papillas and maculas in the youngest patient testified to glaucoma affliction of the papillas. foveal thickening of 279  $\mu\text{m}$  in the right eye and 233  $\mu\text{m}$  in the left eye was also deter-

mined, macular volume was 6.56  $\text{mm}^3$  in the right eye and 11.08  $\text{mm}^3$  in the left eye. Holström et al. (13) tested the suitability of OCT examination in the diagnosis of foveal hypoplasia in children with albinism and with aniridia (as well as specially selected and obtained scans in the case of difficult fixation and nystagmus). In these patients they demonstrated central foveal thickening by means of OCT (expressed by median foveal minimum of 259  $\mu\text{m}$ ) and smaller macular volume (median macular volume 7.00-7.01  $\text{mm}^3$ ) as against a control group of children (median of foveal minimum: median 167  $\mu\text{m}$ , median macular volume 7.10  $\text{mm}^3$ ). They stated that the confirmation of foveal hypoplasia could be of assistance in the diagnosis of isolated congenital aniridia in patients with a mildly expressed phenotype. In a comparison of the only usable OCT finding (the youngest patient of the family we describe) with the above study, central foveal thickening is comparable, in which macular volume is even smaller. With regard to the fact that pathological changes of the cornea frequently occur, the application of local therapy using drops without preservative agents is important. Even any surgical procedure brings with it the risk of "fibrous syndrome" in aniridia, and worsening of keratopathy. Aniridic fibrosis syndrome is characterised by the occurrence of extensive progressive retrolenticular and retrocorneal fibrous membranes. In decision making and choice of the therapeutic procedure, it is therefore necessary to keep in mind all the risks, in order to attain the best vision for the longest possible time. Wearing special contact lenses may also worsen the finding on the cornea. In the case of advanced changes on the cornea, the selection of keratoplasty in order to improve vision is a question for discussion from the long-term perspective, with regard to the potential recurrence of the finding. It is also necessary to take into consideration the incidence of more poorly compensated glaucoma and thus a progressively worsening visual field and vision. A moment of surprise may be the finding on the optic nerve and the retina upon examination of the ocular fundus following renewal of transparency of the optic media after successful keratoplasty or cataract surgery.

In the thirty five year old mother there is a difficult balance in the selection of the procedure to renew transparency of the cornea. This patient had previously be diagnosed with secondary glaucoma, but the ocular fundus has

not been examined since the age of 20 years. It is merely a question of what visual acuity we shall attain by the procedure, and for how long. AAK itself also often worsens following surgical procedures on the limbus or following the application of local antimetabolites in the treatment of aniridia-associated glaucoma (19). As a result, from a long-term perspective the benefit of keratoplasty or transplantation of limbal cells is uncertain for this patient.

## CONCLUSION

Aniridia represents a severe panocular pathology. Seventy percent of diagnosed individuals with isolated aniridia have afflicted parents. In isolated familial aniridia there is a 50% risk of the occurrence of this pathology in the children of an afflicted parent. In exceptional cases, non-ocular sensory manifestations may also appear in these patients, as well as neurological abnormalities or affliction of the pancreas. A reduction of the sense of smell has been described in patients with isolated aniridia. Behavioural disorders and retarded development are rare occurrences (1, 5, 6, 11, 18, 24, 30). With regard to the potential more pronounced variability of the phenotype, genetic examination is important, and its importance is multiplied especially at early childhood age, when it helps to differentiate children with WAGR (Wilms' tumour, aniridia, genital abnormalities, mental retardation) syndrome, manifested so far only through aniridia, from patients with mutation in PAX6. This concerns a progressing pathology, therapy is frequently arduous especially in patients with severely expressed symptomatology. In these patients it is necessary to consider carefully the selection of ocular procedures with regard to the increased risk of subsequent complications. Even if it is stated that symptoms in aniridia are irreversible and progress with advancing age, studies under way at present can nevertheless provide certain hope for those afflicted. Aniridia is linked to insufficient production of PAX6 (as a consequence of haploinsufficiency of PAX6), and as a result Gregory-Evans et al. (9) attempted to influence the dose of PAX6 postnatally in a model in mice. Specific topical administration of ataluren and gentamicin not only halted the progression of the pathology as a consequence of PAX6 mutation, but to a certain degree even reversed certain changes on the cornea, lens and retina.

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