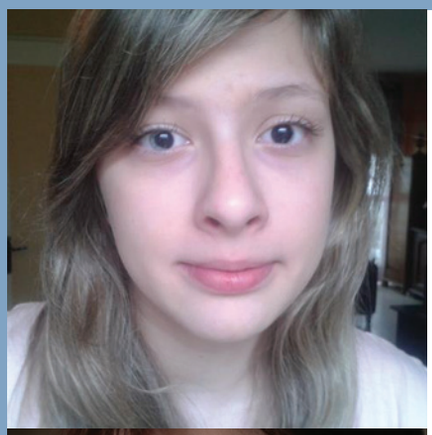
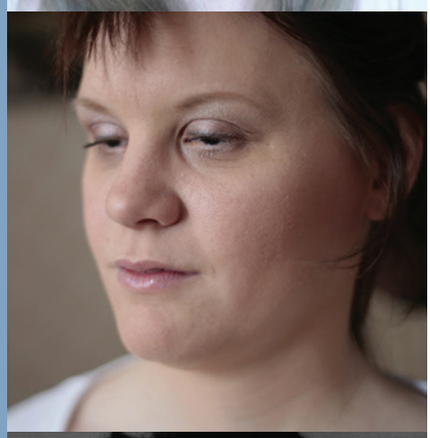
ANIRIDIA EUROPE

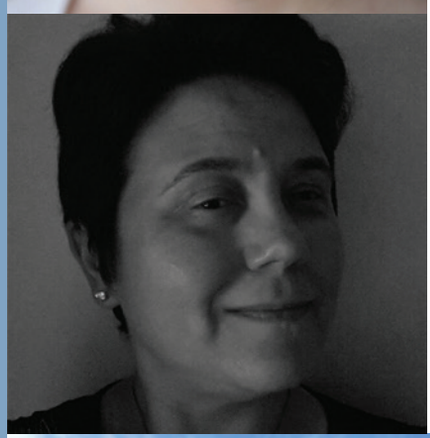
LOOKING OUT FOR THE ANIRIDIA COMMUNITY

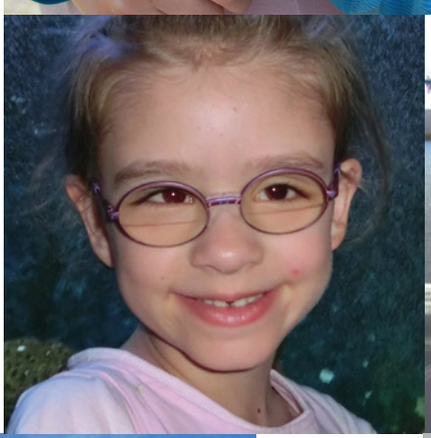
CONGENITAL ANIRIDIA

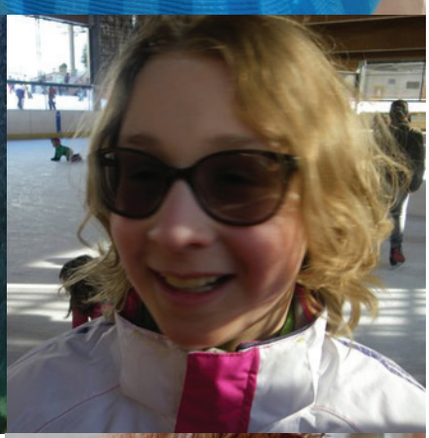
A BROCHURE ABOUT THE RARE EYE CONDITION ANIRIDIA

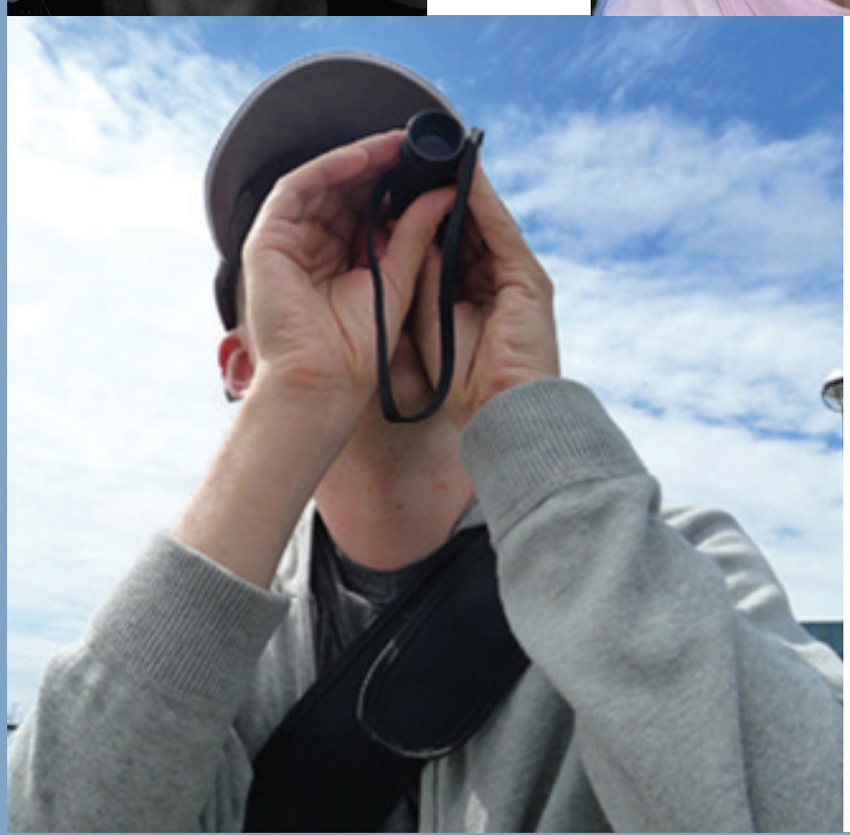


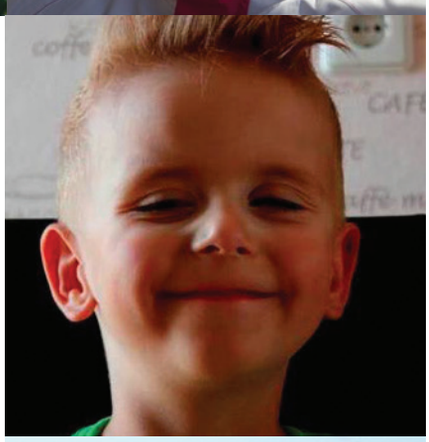












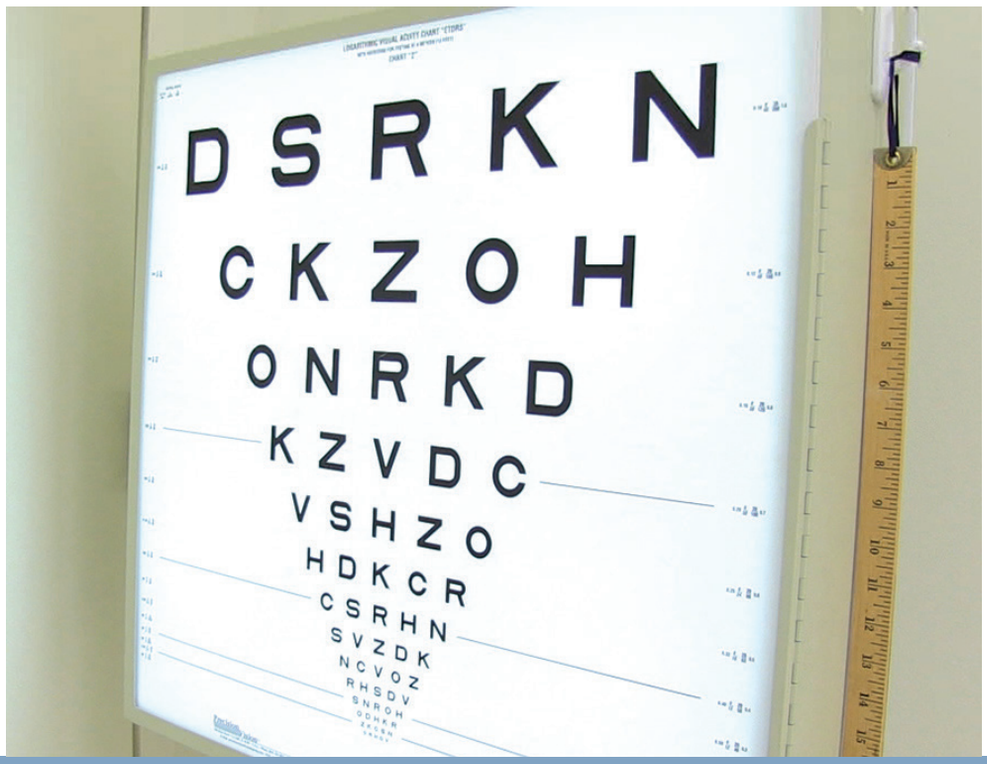
CONTENTS

WHAT IS ANIRIDIA?

Aniridia (from Greek, meaning “without” [an-] and “iris” [-iridia]) is a rare genetic condition affecting primarily the eyes, but depending on the severity and type of genetic disorder it might also have other impacts on human development and health. Aniridia is in most cases caused by mutations in the PAX6 gene and is in about two thirds of the cases hereditary. Aniridia is registered in Orphanet, the reference portal for information on rare diseases and orphan drugs, under the number ORPHA77.

Besides the lack of iris tissue (iris hypoplasia), aniridia also shows alterations of other structures of the eye: cornea, crystalline lens, optic nerve, and retina. The center of the retina which enables detailed vision (fovea) and the optic nerve are often not fully developed (hypoplasia/dysplasia). This causes an inborn deficit of normal visual development and later of fine visual acuity. Therefore, most patients with aniridia have an inborn visual impairment with the typical sign of nystagmus (eye wobbling) which is present in all diseases leading to congenital visual impairment.

During life, aniridic eyes may develop complications, the most frequent being an opacification of the crystalline lens (cataract), a rise of intraocular pressure with subsequent damage to the optic nerve (glaucoma) and opacifications of the cornea. This may lead to a further deterioration of visual acuity.



DIAGNOSING ANIRIDIA

Since aniridia is a genetic disorder, it is present at birth. It is diagnosed by clinical examination and confirmed with genetic testing.

Aniridia is not always picked up by the standard paediatric exams at birth, one week or four weeks following birth. Parents might notice the following peculiarities with their newborn child:

- Unwillingness to open the eyes, crying in bright light
- More willing to open eyes in dimmed light
- Uncontrolled pendular eye movements
- Lack of development of fixation, no social smile
- Lack of iris colour, eyes are black as the colour of the pupil

In any of these signs, an examination by an ophthalmologist (medical doctor specialized in eye care) should be performed quickly. The ophthalmologist will perform the following examinations to confirm aniridia and to evaluate the severity of the congenital findings:

- Examination of the eye movements
  - o Nystagmus / eye wobbling present as a sign of inborn visual impairment?
  - o Does the infant fixate?
- Examination of the anterior segment of the eyes with a loupe or a microscope
  - o Degree of aniridia (partial or complete?)
  - o Is the lens clear or does it show signs of cataract?
  - o Is the cornea clear?
- Examination of the back of the eye with a magnifying glass and light
  - o Does the child have foveal hypoplasia?
  - o Is there a hypoplasia of the optic nerve?
- Measuring of the eye pressure
  - o Is the eye pressure normal or elevated?
  - o This exam has to be performed at least every six months for a lifetime in every an iridia patient!
  - o In newly born or small children it might be necessary to measure the eye pressure under general anesthesia.

Following the diagnosis of aniridia by the ophthalmologist, genetic testing is mandatory to see which genetic mutation has led to aniridia and to check for associated syndromes like the WAGR Syndrome (see next chapter).

GENETICS

As soon as the clinical diagnosis of aniridia is confirmed, genetic diagnosis should be performed.

HEREDITY AND FREQUENCY

Aniridia affects 1:40 000 to 1:100 000 people, males and females equally. Aniridia is most often (50 to 65%) inherited from a parent affected as well (familial aniridia). About one in three cases results from a so-called “de-novo mutation”, meaning the child developed a new mutation while both parents have no aniridia (sporadic aniridia).

Aniridia is transmitted as an autosomal dominant trait. A disorder is referred to as dominant when only one mutant allele is needed to cause it (alleles are the two copies of each gene that are present in every cell of the body). As only one allele from each parent is transmitted to the child, the affected person can consequently transmit the mutation on average to 50% of his or her children, irrespective of the sex of the child.

GENETIC CHANGES

The most frequent genetic alteration in aniridia is a defect (geneticists call them “mutations”) of the PAX6 gene.

Genes lie on ***chromosomes*** where all our hereditary and developmental information is stored. Each human has 23 pairs of chromosomes, and they store hundreds of thousands of genes. ***Genes*** are important for the development of all body parts of the embryo during pregnancy and they influence human development and organ function during the whole life span.

The PAX6 gene is situated on the short arm of the chromosome 11 (11p13). PAX6 regulates the development of the eyes during the 8th to 14th weeks of pregnancy – so aniridia is determined that early and no mother of an affected child needs to worry about having done anything wrong during pregnancy. PAX6 regulates the development of the complete eye, therefore a disturbance of the PAX6 gene function leads to panocular (whole eye) abnormalities, affecting not only the iris but also the cornea, anterior chamber, lens, retina, and optic nerve.

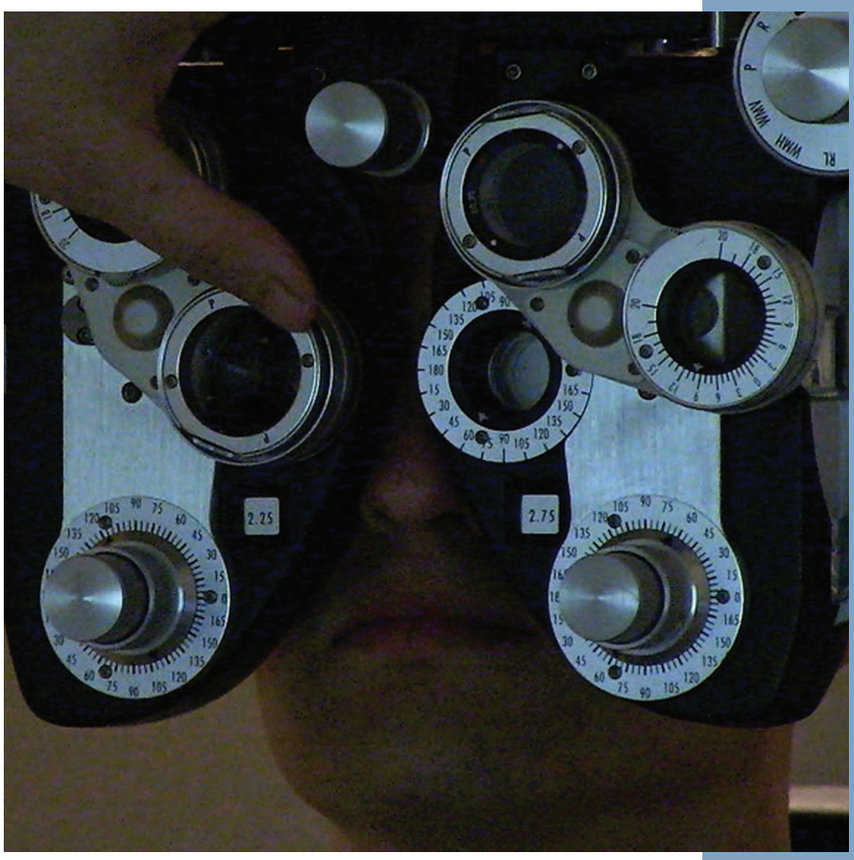
Besides being responsible for eye development, the PAX6 gene is also known to be responsible for the development of other parts of the body, like the kidneys, pancreas, brain, and other areas that are currently being studied.

Therefore, PAX6 mutations can as well be associated with occurrence of diabetes or the tendency of weight gain in aniridia patients.

However, although the majority of aniridia cases are caused by the PAX6 mutations, cases have also been reported with no identified PAX6 mutations.

WAGR SYNDROME

WAGR Syndrome is a rare syndrome associated with aniridia. WAGR means: Wilms-Tumor (a kidney tumor in children), Aniridia, Genito-urinary abnormalities, and mental Retardation. It occurs in 10% of aniridia patients (never in familiar aniridia) and is due to the fact, that besides PAX6 more genes on Chromosome 11 are nonfunctioning. For more information on WAGR Syndrome: http://www.wagr.org/.



In spite of the rareness, every infant and child with aniridia needs to have renal ultrasound exams to rule out kidney tumor up to the definite genetic diagnosis and ruling out WAGR Syndrome.

GENETIC TESTING

Genetic testing is done by sending blood samples of the affected person and perhaps of the parents to specialized laboratories. Here, the focus of genetic testing lies on the PAX6 gene and the neighbouring genes responsible for WAGR Syndrome. Test results may take weeks and up to three months to be finished. The results report the kind of genetic alteration and confirm or disaffirm syndromic aniridia with WAGR Syndrome.

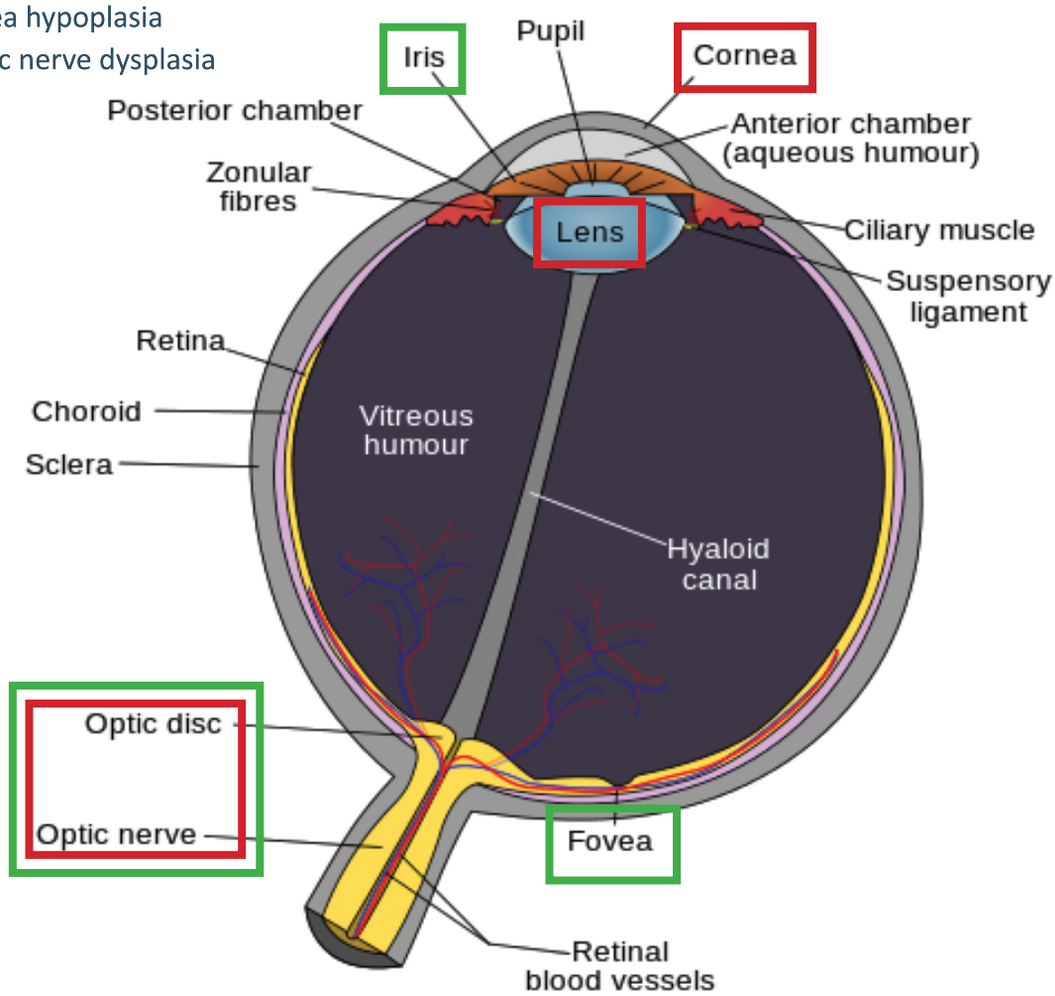
THE EYE IN ANIRIDIA

The eye is a delicate multi-layered organ which “translates” the optic signal into electrical signals which can be understood by the brain. We see/perceive with our brain, but all microscopic parts of the eye are needed to transmit the visual world clearly to the optic nerve.

INBORN

Conditions of the eye, present at birth that are most specific for aniridia patients include (marked green in the diagram):

- Iris hypoplasia
- Fovea hypoplasia
- Optic nerve dysplasia



POSSIBLE LATER ANOMALIES

Later in life complications may occur at the tissues marked in red:

- Corneal haze and opacifications
- Cataract
- Glaucoma with damage of the optic nerve

From the diagram it can be seen clearly that especially the tissues which help the optic signal travel through the eye (cornea, iris, lens) and the tissues which change the optic signal to an electric signal and send it off to the brain (fovea, optic nerve) are affected in aniridia.

LIVING WITH ANIRIDIA

Aniridia affects mostly the eyes: the iris, cornea, intraocular pressure, lens, fovea, and optic nerve. The variability between the two eyes is usually small. Since it is caused by a genetic mutation it is expressed quite individually in each patient. Some people have more medical conditions, others less. The severity of conditions is also individual. Aniridia patients often suffer from:

impaired visual acuity, caused by the underdevelopment of the eye
light sensitivity, caused by iris hypoplasia
nystagmus
cataract (clouding of the lens)
glaucoma (elevated intraocular pressure)
corneal opacification/keratopathy,

where the last three are responsible for progressive visual failure.

IRIS

The iris is a thin, circular structure in the eye, responsible for controlling the diameter and size of the pupil and thus the amount of light reaching the retina. The colour of the iris is often referred to as “eye colour”. The one thing that distinguishes aniridia patients is iris hypoplasia, ranging from almost total to partial lack of the iris or various types of defects. This means that the pupil, responsible for letting the light enter the retina, is most often big. This causes light sensitivity, which is perceived quite individually and can change during one’s lifetime. The lack of the iris or its misfunctioning also affects the possibility to focus, affecting a person’s vision. In addition, the iris protects the eye from the dangerous UV light that can damage the vision and cause cataracts to develop.

People with aniridia usually find it difficult to adapt to rapidly changing light conditions. They may be sensitive to intense light and reflections from windows, mirrors and wet, metallic or white surfaces and often have to adapt their home, work and school environments accordingly.

Glare caused by reflections may lessen the ability to see details or cause visual discomfort, dry sneezing and headaches. Moving from inside to outside, from shadow to sunny places, switching lights on and off, moving in foggy or cloudy days, and crossing in front of car headlamps can produce a painful dazzling that reduces visual acuity and causes uncertainty in movement.

WHAT CAN BE DONE?

Light sensitivity can be solved with appropriate sun glasses that completely filter out the damaging UV light. The type and level of shading is very individual and depends on both the patient's level of light sensitivity and weather conditions. "Blue blockers" and polarised lenses have been reported by aniridia patients to be more pleasant for the eyes. "Blue blockers" block away the blue light from the light spectra, making objects appear clearer, sharper, and well defined. Polarised glasses take away the glare. The UV filter protects the eyes and lowers the risk for cataract development. Due to varying light conditions which depend on the weather and time of the day/season of the year, one might need to have several sunglasses with varying shading levels. Some aniridia patients have had positive experiences with photochromic lenses, in combination with blue light blockers and UV filter. Photochromic lenses are lenses that darken on exposure to specific types of light, most commonly ultraviolet (UV) radiation. There are lenses that start from being clear when not exposed to UV light and there are those that from the beginning already have a certain percent of shading. The level of shading increases depending on the level of UV light that they are exposed to.

Besides protecting the eyes from the light, sunglasses also to some extent protect the cornea from the wind and dust or accidental intrusion of foreign objects.

In addition to the glasses, one can also use artificial lenses, with an artificial iris. There are two available methods, one is permanent and requires a surgical intervention, whereas the other is to use contact lenses with iris shading. There are advantages and disadvantages of both. A surgical intervention might damage the highly sensitive cornea, while providing a shield to the macula and more light comfort to the patient. The contact lenses have reported protection to the ocular surface by maintaining moisture between the lens and the ocular surface, but some patients have reported discomfort in using them. Due to the highly sensitive cornea of aniridia patients it is important to carefully reconsider if any of these two options would be relevant for the patient.

FOVEA

Fovea is the part of the eye located in the centre of the macula region of the retina. It is responsible for the sharp central vision, providing ability to see details, usually needed for example for reading or driving. Foveal hypoplasia (under development) is usually present in aniridia patients, from reduced foveal reflex, macular hypopigmentation, and crossing of the usual foveal avascular zone by retinal vessels. The level of the fovea's development has direct effect on the visual acuity and is quite individual in aniridia patients, usually being 20/100 to 20/200. In some individuals, however, fovea is normal resulting in good vision. Foveal hypoplasia causes nystagmus (constant involuntary movement of the eyeball), present in most aniridia patients. Nearly all patients have elevated myopia, a further factor in reduced vision.
Rare cases of complete retinal detachment have been described. Though this has not been linked to genetic causes, lipid accumulations in the outer retinal periphery have been observed in such patients.

OPTIC NERVE

The optic nerve is responsible for transmitting visual information from the retina to the brain. Optic nerve abnormalities such as hypoplasia (for example the optic nerve head appears abnormally small) and coloboma can be detected in some aniridia patients, resulting in lower visual acuity. One of the most common injuries to the optic nerve is from glaucoma (caused by high intraocular pressure), which has high incidence in aniridia patients. Therefore it is very important to regularly follow up the intraocular pressure.

CORNEA

The cornea is the transparent front part of the eye that covers the iris, pupil, and anterior chamber. The cornea, with the anterior chamber and lens, refracts light, with the cornea accounting for approximately two-thirds of the eye's total optical power.

The cornea is composed of five layers, from the outermost to the inner layer: epithelium, Bowman's membrane, the stroma, Descemet's membrane, and the endothelium. The cornea works mainly as a positive lens that, together with the lens, converges the light rays, focusing them on the retina. This is possible thanks to its transparency and resistance. The transparency of the cornea is maintained by the tear film, a complex system that helps to protect and nourish the ocular surface. Research has shown that the quality of the tears of aniridia patients is not as of a normal eye and therefore can be responsible for the development of problems with cornea, corneal degeneration, also known as keratopathy. Research in Sweden has found visible keratopathy in 80% of studied patients, where in 26% of the eyes it created visual disturbances. The same study found that intraocular surgery can trigger the development of keratopathy as well as increase the severity of existing keratopathy. In aniridia patients problems with the cornea occur over time, being transparent at birth but losing its transparency with the years. The process is quite individual and scientists still find it difficult to understand the progression of the disease. Dry eyes and tear quality is associated with the status of the cornea.

WHAT CAN BE DONE?

Problems with the cornea create great challenges for the researchers. It is believed that trying to avoid the development of corneal problems is one of the key priorities of treatment of aniridia patients and should be the main focus of future research. It is important to deal with the disease in the early stages, before its progression.

Medication, such as lubricants, mucolytics, and punctual occlusion can be used for ocular surface disease. Preservative-free and phosphate-free gel (topical treatment) and nourishing ointment for cornea (like dexpanthenol preservative-free ointment) should be used. For severe disease corneo-limbal transplant surgery can be undertaken but carries a high risk of failure and may require lifelong systemic immunosuppression. Other treatments are also available but require careful consideration and decision based on each individual case.

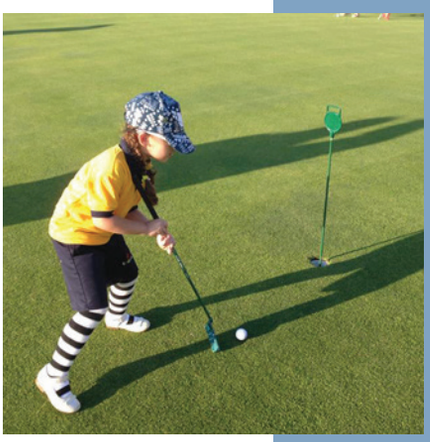
CATARACTS

A cataract is a clouding of the lens inside the eye which leads to a decrease in vision. In aniridia patients there is a high risk of developing cataracts during lifetime, though there are cases of congenital cataracts (present at birth). Ultraviolet (UV) radiation, coming from the sun or some types of light bulbs, is absorbed by the lens of the eye and can lead to the formation of free radicals inside the lens. Over time, free radicals may damage the lens, causing cataracts. Some drugs, such as corticosteroids, can induce cataract development, and should therefore be used with high care.

WHAT CAN BE DONE?

Sunglasses with 100% UV protection are advised. Cataract extraction may improve visual acuity in patients with dense cataracts, though the visual acuity is still affected by other aspects, like foveal hypoplasia and optic nerve abnormalities. Therefore one should weigh the benefits of a surgery bearing in mind that surgery might have negative effects on the cornea.

GLAUCOMA



Glaucoma is a condition that causes damage to the eye's optic nerve and gets worse over time, if not treated. It is often directly associated with a buildup of intraocular pressure, which can damage the optic nerve. If damage to the optic nerve from high eye pressure continues, glaucoma will cause permanent loss of vision. Without treatment, glaucoma can cause total permanent blindness.

WHAT CAN BE DONE?

Glaucoma is initially treated with topical anti-glaucoma medication; refractory cases may require surgery (trabeculectomy or drainage tube surgery) or cyclodiode treatment. Preservative-free drops should be used to avoid ocular surface toxicity.
Due to the massive corneal complications one should aim at using as few glaucoma drops as necessary and instead consider other options, like performing trabeculotomy instead of installing five sorts of drops per day.

IMPORTANT THINGS TO THINK ABOUT

Several European countries (Spain and Italy, with others to follow) have developed guidelines for clinical management of congenital aniridia. They are comprehensive documents that provide a useful tool for physicians, researchers in clinical and basic science, professionals working in public health and social care, patients and their families, with a view to update knowledge, improve the quality of care, the coordination of actions and related policies and planning. As a general rule it is important to:

- have regular check-ups
- always protect the eyes from dangerous light (UVA, UVB), wind and preservatives in medication
- ask for a second opinion before significant interventions in the eyes

On the next page is a table with summarised aspects regarding regular ophtamological examinations, treatments, prevention of complications and additional things that might help in daily life, depending on the age group. These should be taken as a guidance where national guidelines are missing.

Visual and technical aids may help people with aniridia to perform the same activities in different environments and situations as the rest of the population.

EARLY INTERVENTION

Visual development is a learning process of the first 6 years. Even in the presence of an inborn visual disability this learning process can lead to substantial visual improvement if these conditions are met:

- Optimization of refractive errors, glare by spectacles
- Use of early vision intervention services
- Start as early as possible

Early visual intervention is a support and educational system for very young children (aged birth to six yrs) who are at high risk for developmental delays due to severe visual impairment. The aim is to assist child and family to maximize their child's physical, cognitive, and social/emotional development.

Early intervention needs to be transdisciplinary to ensure all aspects of development are cared for. Services include:

- Special instruction includes designing learning environments and activities that promote the child's development and providing families with information, skills and support.
- Vision services provide identification of children with visual disorders or delays and providing services and training to those children.
- Occupational therapy is added with services that relate to self-help skills, adaptive behaviour and play, as well as sensory, motor and postural development.

IMPORTANT THINGS TO THINK ABOUT DEPENDING ON AGES

	Examinations at the ophthal-mologist (no complications)	What should be checked? (level of detail is different for different age)	Treatment to improve vision quality	Prevention of complications (the most important aspects)
0 – 2 years	‣ Every 3-4 months	‣ Visual acuity ‣ Orthoptic evaluation ‣ Anterior segment ‣ Posterior segment ‣ Retinoscopy ‣ In case of glaucoma visually evoked potentials and visual fields should be investigated	‣ Refraction ‣ UV-blocking glasses for inside and outside ‣ Early visual support activities	‣ Each visit: measurement of the eye pressure. It might be necessary to do it under general anesthesia. In that case it is not performed so often. ‣ Nightly application of nourishing ointment for the cornea (dexpanthenol preservative-free ointment)
2 – 8 years	‣ Every 6 months		‣ Keep dioptric values up to date ‣ See above	‣ See above ‣ First low vision aids can be used from age 5
8 – 18 years	‣ Every 6-8 months		‣ See above ‣ Low vision aids for school	‣ Treatment of elevated eye pressure should be started as early as it is detected ‣ No laser surgery if eye drops are not sufficient for lowering eye pressure
Adults	‣ Yearly, in case of upcoming problems shorter time spans		‣ See above ‣ Check-ups depend on the kind of complications	‣ Often more than one specialist is needed! ‣ See a corneal specialist ‣ See a glaucoma specialist
For all age groups				
If surgery planned	‣ **Think twice** ‣ Make sure you understand every aspect of what your ophthalmologist explains ‣ Do not hesitate to ask questions ‣ Do not hesitate to consult another specialist for a second opinion ‣ Ask your national aniridia group or contact Aniridia Europe			
Always beware of or take second opinions if the following things are suggested	‣ Wearing contact lenses ‣ Wearing contact lenses with iris prints ‣ Implantation of an artificial iris. This procedure might damage the aniridic eye and any residual vision ‣ Use of eye drops which include conservation agents ‣ Use of eye drops which contain phosphates ‣ Laser surgery. No laser surgery for glaucoma if eye drops cannot control eye pressure sufficiently as this might harm the aniridic eye. Perforating surgery like "trabeculotomy" to facilitate the outflow of fluid of the anterior chamber should be used. Possibly more than one surgery is necessary. Other surgeries are available if trabeculotomies are not effective enough. ‣ Decrease the number of examinations per year. If glaucoma has been identified, eye pressure should be measured every three months in any patient of any age.			
Additional things which help to live with aniridia				
0 – 2 years	‣ Get in touch with your national Aniridia Support Group or Association ‣ Get connected to Aniridia Europe ‣ Share experiences with other parents and learn from parents with older children ‣ Ask about the regulations in your country for allowances for children with disabilities and apply for them			
2 – 8 years	‣ Start to be a contact person for parents with younger children and give back help and advice you received when your child was very young			
8 – 18 years	‣ Young persons can participate in aniridia meetings to get to know other youngsters with similar condition ‣ Practice sports with other visually challenged persons			
Adult	‣ Get involved in your national Aniridia association/support group ‣ Share your experiences with others that have aniridia on treatments, visual aids, etc. ‣ Follow latest research			

ROUTINE CHECK-UPS

Routine check-ups in older aniridia persons always include the above mentioned basic examination techniques plus – depending on the occurrence of complications – may include the following tests:

Optical Coherence Tomography OCT

o A laser examination to evaluate the development of the fovea and of the optic nerve

Ultrasound biomicroscopy

o This can evaluate the residual iris and it serves to exam the back of the eye (retina) in patients who have cataract or corneal opacification which prevent a clear view into the eye

Visually Evoked Potentials (VEP)

o They help to evaluate any damage to the optic nerve by glaucoma and are an important follow-up in aniridics who suffer from aniridic glaucoma

Visual field testing

o This is important to evaluate whether high intraocular pressure (glaucoma) has damaged the peripheral visual field. This as well should be done regularly in aniridics who suffer from aniridic glaucoma.

Corneal topography

o They produce a kind of map of the corneal surface, determining the degree of impact that corneal opacifications have.

IT IS NOT ALL ABOUT THE EYES

Since aniridia is most often caused by genetic mutation, its expression is quite individual, from a single symptom to several, ranging from mild to severe manifestation. In some cases symptoms include problems with neuropsychology, urology and gynaecology, endocrinology, and orthopaedics, such as diabetes, central auditory processing disorder (difficulty with discriminating and interpreting sounds), decreased or absent sense of smell, obesity and autism.

The USA-based Non-Governmental Organisation Aniridia Foundation International defines aniridia as a syndrome, since it has been recognised that aniridia most often involves several medical issues besides not having an iris. This is an area that requires further research.

ANIRIDIA EUROPE

Aniridia is a very rare disease and every family affected is often alone to face the diagnosis. Aniridia Europe, the federation of European aniridia associations and representatives, has been founded to change this situation.
The main objective of Aniridia Europe is to create a platform for cooperation between European national associations, support groups and networks, individuals with aniridia and their families, as well as researchers and professionals working with aniridia and related conditions.
In addition, the objectives of Aniridia Europe are to:

- collaborate in spreading proper and correct information on aniridia and the best available treatments
- support and inspire research by creating scientific interest on aniridia and associated conditions and connecting professionals both at local and international level
- promote the development of national and international guidelines on aniridia
- encourage people affected by aniridia to create associations in other countries

In order to achieve its objectives Aniridia Europe is supported by a Scientific Committee comprised of distinguished experts in the aniridia field.
Aniridia Europe is a full member of EURORDIS, a non-governmental patient-driven alliance of patient organisations and individuals active in the field of rare diseases in Europe and beyond.

FURTHER INFORMATION AND CONTACT:

www.aniridia.eu
f: www.facebook.com/AniridiaEurope

Inquiries to the federation should be sent to **post@aniridia.eu**, or use the contact form provided at the Aniridia Europe web-page.

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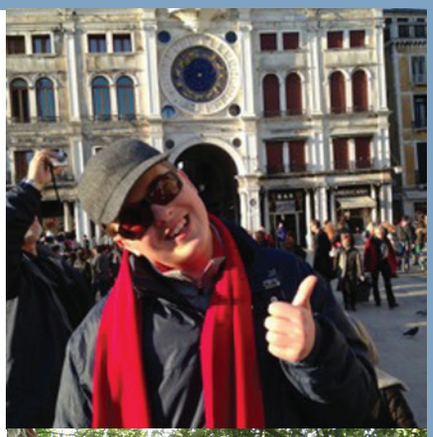
SUPPORT US

We believe that collaboration between organisations of patients and medical doctors, healthcare institutions, research centres, the corporate sector and relevant stakeholders is beneficial for all parties and necessary for development within the domain of rare diseases, where resources are limited. As an NGO (Non-Governmental Organisation) we have a subsidiary role in society, but we need funds to carry out our activities as we do not receive government funding. There are several ways you can support us, from making a donation, getting involved as an individual, a researcher or an organisation, or by including Aniridia Europe in your last will and testament.

Please consider a donation through Aniridia Europe to aniridia-related research. Private donations are often essential for developing research within the field of rare diseases.

Did you know?

Sharon Stewart, born with sporadic Aniridia, donated millions of dollars to research related to aniridia and Pax6. The research includes general research to understand different conditions related to Aniridia, gene therapy, surgery techniques, and a drug therapy protocol, with great promise of success, that has reached human clinical testing. In addition, thanks to the financial support from the Sharon Stewart's Trust a number of international meetings and conferences on aniridia have been organized, including the the second European Conference on Aniridia.



CREDITS

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ANIRIDIA EUROPE - THE FEDERATION OF ANIRIDIA ASSOCIATIONS AND NETWORKS ACROSS EUROPE