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GENETICS

Mild aniridia phenotype: an under-recognized diagnosis of a severe inherited ocular disease

Claudia Yahalom[1] · Anat Blumenfeld[1] · Karen Hendler[1] · Orly Wussuki-Lior[1] · Michal Macarov[1] · Mordechai Shohat[2,3] · Samer Khateb[1]

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Abstract

Purpose Aniridia is a rare panocular disorder caused by mutations in the *PAX6* gene and characterized mainly by iris hypoplasia. Here, we present six families with a history of low vision/blindness with a previously undiagnosed mild aniridia phenotype with minimal iris changes.

Methods Retrospective case series of patients diagnosed with a subtle aniridia phenotype characterized by minimal iris abnormalities, foveal hypoplasia, and an identified mutation in *PAX6*. Data collection from patient's charts included ocular examination findings, visual acuity, refraction, and clinical pictures when available. Genetic analysis was performed by isolation of genomic DNA from peripheral blood. The main outcome was the identification of patients with mild aniridia harboring a *PAX6* mutation.

Results In all six families, the phenotype included minimal corectopia and foveal hypoplasia; nystagmus was present in 10 out of 11 patients. A *PAX6* mutation was identified in all six families; three of these mutations were identified previously, and three are novel mutations. All the mutations are located within the conventional 128-residue paired domain of *PAX6*.

Conclusions A mild form of aniridia should be considered in the differential diagnosis of patients with low vision associated with mild iris abnormalities, nystagmus, and foveal hypoplasia. To ensure an accurate diagnosis of aniridia, minimal pupillary changes and/or incipient keratopathy should be examined. The broad phenotypic heterogeneity among aniridia leads to the fact that eye care clinicians must have a high index of suspicion for the disease when seeing undiagnosed low vision patients, because proper diagnosis can improve management as well as facilitate genetic testing and counselling.

Keywords Aniridia · Mild phenotype · *PAX6* · Corectopia

Introduction

Aniridia (OMIM 106210) is a panocular genetic disorder characterized by iris hypoplasia combined with foveal hypoplasia, resulting in severely reduced visual acuity and nystagmus. Aniridia usually first presents in early infancy and is often associated with other, typically later-onset ocular abnormalities, including cataract, glaucoma, and keratopathy [1–3]. Approximately two thirds of all cases are familial with autosomal dominant inheritance, whereas the remaining one third of cases present as a sporadic form.

Although most cases of aniridia occur as an isolated ocular disorder, a small subset of sporadic cases occurs as part of either WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) or Gillespie syndrome (aniridia, cerebellar ataxia, and mental retardation) [3]. The most characteristic ocular abnormality associated with aniridia is iris hypoplasia; in severe cases, the iris may be reduced to a small stump of residual tissue, making the diagnosis relatively straightforward. In mild cases, the entire iris may still be present, with only transillumination defects or an abnormal surface architecture, partial iris defects (resembling a coloboma), an eccentric or misshapen pupil, or iris ectropion (ectropion uveae) [4–7]. In these mild phenotype cases of aniridia, the diagnosis can be easily overlooked or delayed. Visual acuity can range from moderately to severely reduced, even among siblings [8]. In particular, the ocular surface

✉ Claudia Yahalom
kloudia@hadassah.org.il

[1] Department of Ophthalmology, Hadassah-Hebrew University Medical Center, 91120 Jerusalem, Israel

[2] Medical Genetic Institute, Maccabi Health Services, Tel Aviv, Israel

[3] Bioinformatic Department, Cancer Center, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv-Yafo, Israel

Table 1 Clinical characteristics of the *Pax6* affected subjects with a history of mild aniridia

Family number	Patient number	Age (years)	Binocular BCVA (Snellen)	Nystagmus	Foveal hypoplasia	Iris abnormalities	Cornea	Cataract	Refraction (*D*)
1	II-2	35	20/40	−	+	Corectopia and small iris coloboma	NV	+	− 0.50 BE
	III-1	10	20/80	+	+	Corectopia	NV	−	− 1.00 BE
2	II-3	20	20/500	+	+	Sectorial iris atrophy, ectropion uvea, and iris coloboma	NV	−	− 17.00 BE
	I-1	54	20/160	+	+	Corectopia and iris atrophy	NV-advanced	+	NA
3	III-1	5	20/200	+	+	Corectopia	NV	−	− 4.50 BE
	II-1	35	20/200	+	+	Corectopia	NV	+	NA
	II-4	40	20/100	+	+	Corectopia	NV	−	NA
4	I-2	75	20/250	+	+	Iris coloboma	NV-advanced	+	NA
	II-1	3*	20/200	+	+	Corectopia and isolated transillumination	Normal	−	+ 8.00 BE
5	II-1	2	CSM	+	+	Corectopia	Normal	+	+ 7.00 BE
6	II-3	21	20/50	+	+	Corectopia	NV	−	− 5.00 BE

+ present; − absent, *BCVA* best-corrected visual acuity, *CSM* central, steady, and maintained fixation, *NV* neovascularization, *S/P* status post, *Refraction* mean spherical equivalent of BE in diopters

*age at last exam

can be severely affected by a progressive pathology known as aniridia-associated keratopathy, thereby contributing significantly to impaired vision [3–6, 9–11].

The *PAX6* locus-specific database currently contains 472 unique sequence variants scattered throughout the gene (http://lsdb.hgu.mrc.ac.uk/home.php?select_db=PAX6, accessed December 2017). About 80% of these variants are predicted to disrupt either transcription or translation and are therefore likely to be pathogenic. The remaining 20% introduce an amino acid substitution (i.e., a predicted missense mutation).

Here, we report six families with a history of low vision and extremely subtle anterior segment anomalies; four of these families were undiagnosed for several generations. We identified a total of six distinct mutations in *PAX6* gene in these families, five missense mutations and one frameshift, three of them being novel.

Materials and methods

Patient recruitment

In this retrospective case series, the medical records of patients diagnosed with mild aniridia and an identified mutation in *PAX6* gene were included. The main outcome was the identification of patients with minimal iris/corneal changes and foveal hypoplasia, as well as the identified mutation in the *PAX6* gene. This study was approved by the Institutional Review Board at Hadassah-Hebrew University Medical Center.

Referral base Our institute is a national referral center for the diagnosis and rehabilitation of patients suffering from low vision. It is a multidisciplinary clinic located at a tertiary hospital and its team consists of optometrists, ophthalmologists, social worker, and genetic counselor. The patients were recruited between the years 2013 and 2017.

Clinical evaluation

Data from patient files was collected including best-corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure, and fundus examination (Table 1). Retinal optical coherence tomography (OCT) and anterior segment photography were included when available. Genetic tests results were obtained following isolation of genomic DNA from peripheral blood drawn from all participants according to standard protocols [3]; the results are summarized in Table 2.

Sanger sequencing and whole-exome sequencing (WES)

To screen for mutations in *PAX6* gene, Sanger sequencing was performed using specific primers designed with Primer3 (http://primer3.ut.ee/). WES analysis was performed for the index case in Family 4 and the parents at Centogene (Rostock, Germany) with coverage depth > 100× (see Table 3). The samples were processed on the Ion Proton Platform (Life Technologies), with approximately 33 Mb of coding exons covered as described by Consensus Coding Sequences. All disease-causing variants reported in HGMD, ClinVar or CentoMD (class 1 and 0), as well

Table 2 Mutations identified in *PAX6* gene in the six studied families

Family number	Reason for referral	Number of affected generations	Mutation type	Exon	Mutation cDNA (c.) Protein (p.)	ExAc prevalence	Mutation taster	PolyPhen-2	SIFT	GVGD	Reference
1	Congenital cataract	3	Missense	5	c.97G>C p.(Ala33Pro)	0	Disease causing (1)	Probably damaging (1)	Deleterious (0.02)	C0	12
2	Familial blindness	2	Deletion	6	c.233_241del p.(Val78_Pro81delinsAla)	0	Disease causing (0.980)				7
3	Isolated foveal hypoplasia	3	Missense	6	c.233T>G p.(Val78Gly)	0	Disease causing (1)	Probably damaging (1)	Deleterious (0)	C65	Novel
4	*PAX6* mutation per WES	1	Missense	6	c.154T>C p.(Cys52Arg)	0	Disease causing (1)	Probably damaging (1)	Deleterious (0)	C65	13
5	Congenital cataract	1	Missense	5	c.38G>T p.(Gly13Val)	0	Disease causing (1)	Probably damaging (1)	Deleterious (0)	C0	Novel
6	Nystagmus	2	Missense	7	c.383G>A p.(Arg128His)	0	Disease causing (1)	Probably damaging (0.983)	Deleterious (0.03)	C0	Novel

Mutations were annotated according to *Homo sapiens* paired box 6 (PAX6), transcript variant 1, mRNA, NCBI Reference Sequence: NM_000280.4. ExAc, Exome Aggregation Consortium- http://exac.broadinstitute.org/; Mutation Taster- http://www.mutationtaster.org/; PolyPhen-2, Polymorphism Phenotyping- http://tux.embl-heidelberg.de/ramensky/; SIFT, Sorting Intolerant From Tolerant- http://sift.jcvi.org/ and Align GVD- http://agvgd.iarc.fr/

WES whole-exome sequencing, *ExAc* Exome Aggregation Consortium

Table 3 WES analysis summary of the affected subject and both parents in family 4

Subject	Number of mapped reads	Percentage of on-target reads (%)	Number of amplicons	Average reads per amplicon	Percentage of amplicons with at least 20 reads (%)
Mother	40,722,870	96.33	293,903	132.1	93.45
Father	40,758,934	94.55	293,903	131.1	93.45
Proband	77,499,589	84.50	293,903	249.4	95.55

as all variants with a minor allele frequency < 1% in the ExAc database, were considered. Mutations were named according to NCBI Reference Sequence: NM_000280.4 (PAX6 transcript variant 1).

Results

Eleven patients in six unrelated families were included in our analysis (Figs. 1, 2, and 3). All patients presented with subtle iris irregularities and foveal hypoplasia. Among nine patients who were older than 2 years of age, seven had low vision and nystagmus. In addition, 5 out of 11 patients had a cataract and 9 presented with keratopathy. None of the patients had glaucoma at the time of diagnosis. The clinical characteristics of the affected members in each family are summarized in Table 1. All the identified mutations are located within the conventional 128-residue paired domain of *PAX6* (Table 2).

Family 1

The index case in this family was a 35-year-old male (II:2, Fig. 3) who was referred to our institute for genetic counseling with a diagnosis of congenital cataract. In his 20s, this patient underwent cataract surgery in one eye. In addition to the presence of cataract, our examination revealed corectopia with a small iris coloboma, as well as mild peripheral corneal vascularization (Fig. 1a) and foveal hypoplasia in both eyes. Family history revealed that this patient's mother, sister, and niece also had low vision and nystagmus (Fig. 3). His niece (III:1) also underwent a complete eye examination, which revealed corectopia, mild corneal vascularization, and foveal hypoplasia in both eyes (Table 1). No other members of this family were available for ocular or genetic testing. Due to the additional clinical findings and cataract history, we suspected that affected members of this family had a mild aniridia phenotype. Thus, the entire *PAX6* gene was sequenced in the index case, revealing a missense mutation, c.97G>C (p.(Ala33Pro)) (Table 2); this mutation has been reported previously [12].

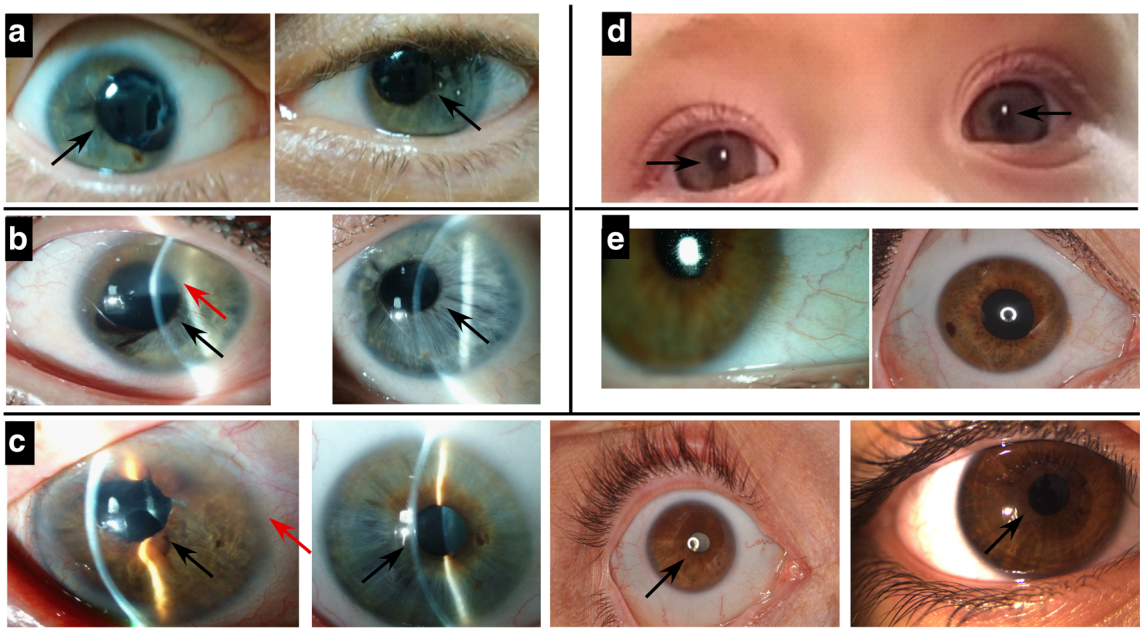

Fig. 1 Anterior segment findings in affected members of the indicated families. Corectopia (in the direction of pupil displacement) is indicated by black arrows, and advanced corneal vascularization is indicated by red arrows. **a**–**e** Families 1, 2, 3, 5, and 6, respectively. See also Table 1

Family 2

The index case in this family was a 20-year-old female (II:3) who was legally blind and had nystagmus, with no clear diagnosis. She had a family history of oculocutaneous albinism and low vision (Fig. 3). She underwent genetic counseling and a thorough eye exam, which revealed normal pigmentation, fine peripheral corneal vascularization, iris atrophy, and foveal hypoplasia in both eyes, as well as a small iris coloboma in her left eye (Fig. 1b). Her mother (I:1) was also examined and was found to have bilateral corectopia, iris atrophy, corneal neovascularization, and foveal hypoplasia (Table 1).

These findings led to the suspicion of a mild form of aniridia, and they were referred for sequencing of the *PAX6* gene, which revealed a 9-bp deletion, c.233_241del (p.(Val78_Pro81delinsAla)) (Table 2). A description of the extended family was described previously as a combined phenotype of two genetic forms of eye disease [7].

Family 3

III:1 (index case) was 5-year-old female when referred to our low vision rehabilitation service due to poor vision and nystagmus. She had a known mutation in the *PAX6* gene identified elsewhere due to a family history of foveal hypoplasia in her mother (II:1) and maternal aunt (II:4), both of whom had a previously unpublished mutation in *PAX6*; c.233T>G, (p.(Val78Gly)) (Table 2, Fig. 3), predicted to be pathogenic by bioinformatics tools. Genetic analysis revealed that the index case harbor the same mutation in *PAX6*, although her previous eye examinations were normal (with the exception of nystagmus). A comprehensive eye examination at our institute revealed a slight corectopia, mild corneal neovascularization (Fig. 1c), and clear evidence of foveal hypoplasia. In addition, ocular examinations of the mother of the index case and aunt revealed mild corectopia and mild corneal neovascularization that had not been observed in previous examinations. Her maternal grandfather (I:2) was also examined due to a long history of low vision; this exam revealed bilateral advanced corneal vascularization and corneal opacity, as well as foveal hypoplasia (Table 1). In this family, the mutation in *PAX6* was linked to a mild form of aniridia, and not simply to foveal hypoplasia as previously believed.

Family 4

A 9-month-old girl (II:1) was referred to our clinic due to nystagmus and a known mutation in *PAX6* gene using WES analysis, which was performed previously upon the request of her parents in an attempt to identify the putative genetic cause of the nystagmus (Table 3 and Fig. 3). Her history revealed nystagmus and mild hypotonia, which were diagnosed when she was several weeks old. A brain MRI was normal. Repeated eye exams were also reported as normal. WES analysis identified a previously reported [13] de novo missense mutation, c.154T>C (p.(Cys52Arg)), in one allele of the *PAX6* gene Table 2); both parents were negative for this mutation. We re-examined the index case (II:1) and found an

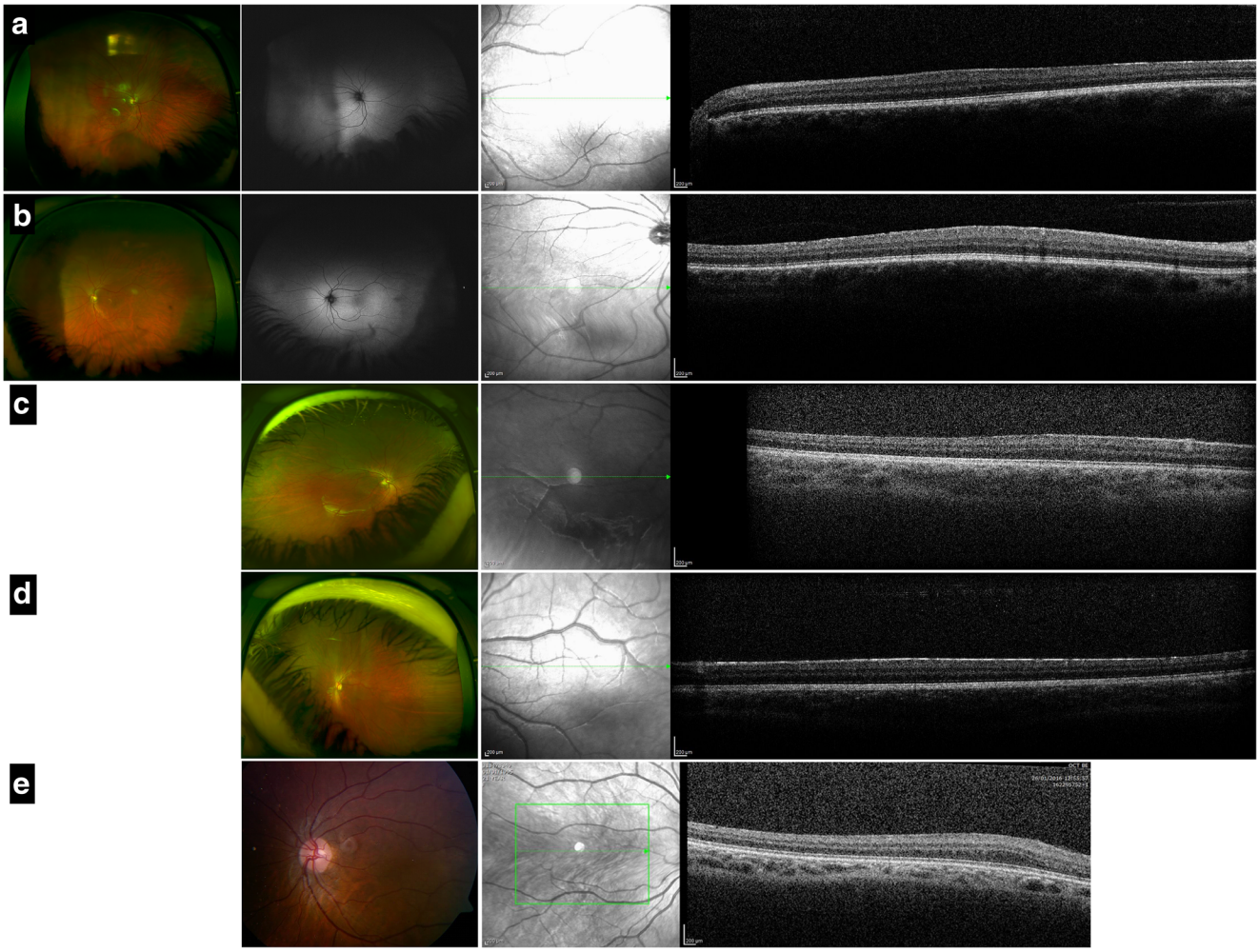

Fig. 2 Fundus findings in patients harboring *PAX6* mutations causing subtle aniridia**. a** Right eye (RE) and **b** left eye (LE) of II:1 in family 3. Ultra-wide field pseudocolor (Optos) and short-wave autofluorescence (SWAF) fundus photos show diminished macular reflex due to foveal hypoplasia. Corresponding SD-OCT horizontal cross-sections show absence of foveal pit. **c** RE and **d** LE of the index case III:1 in family 3. Optos fundus photos and SD-OCT cross sections demonstrate similar foveal hypoplasia as seen in her mother. **e** LE color fundus photo of II:3 in family 6 and the corresponding SD-OCT cross section show foveal hypoplasia also in this patient

extremely mild form of corectopia and foveal hypoplasia, neither of which was observed previously (Table 1). Once again, we attributed this mild phenotype to a mild case of aniridia.

Family 5

A 2-year-old male (II:1) who was referred for genetic counseling due to a diagnosis of congenital cataract and nystagmus. A brain MRI was normal. A thorough eye exam revealed slight corectopia (Fig. 1d) with isolated dot-like transillumination defects, localized posterior capsular cataract, and foveal hypoplasia (Table 1). These findings led to *PAX6* gene sequencing, which revealed a novel mutation, c.38G>T (p.(Gly13Val)) (Table 2), expected to be disease causing according to the bioinformatic prediction tools. His parents also underwent genetic and ocular testing, which revealed that the mother (I:1) has a mosaic germline mutation and a normal ocular examination (Fig. 3).

Family 6

A 21-year-old female (II:3) had been followed by our low vision clinic since a young age due to nystagmus and foveal hypoplasia. Family history revealed that both her father (I:2) and her paternal uncle (I:3) also had nystagmus and decreased vision. Unfortunately, neither family member was available for an eye exam. During the index case last exam, slight corectopia and fine peripheral corneal neovascularization were noted in addition to the previously identified foveal hypoplasia (Table 1, Figs. 1e and 2). She was referred for sequencing of the *PAX6* gene, which revealed a novel missense

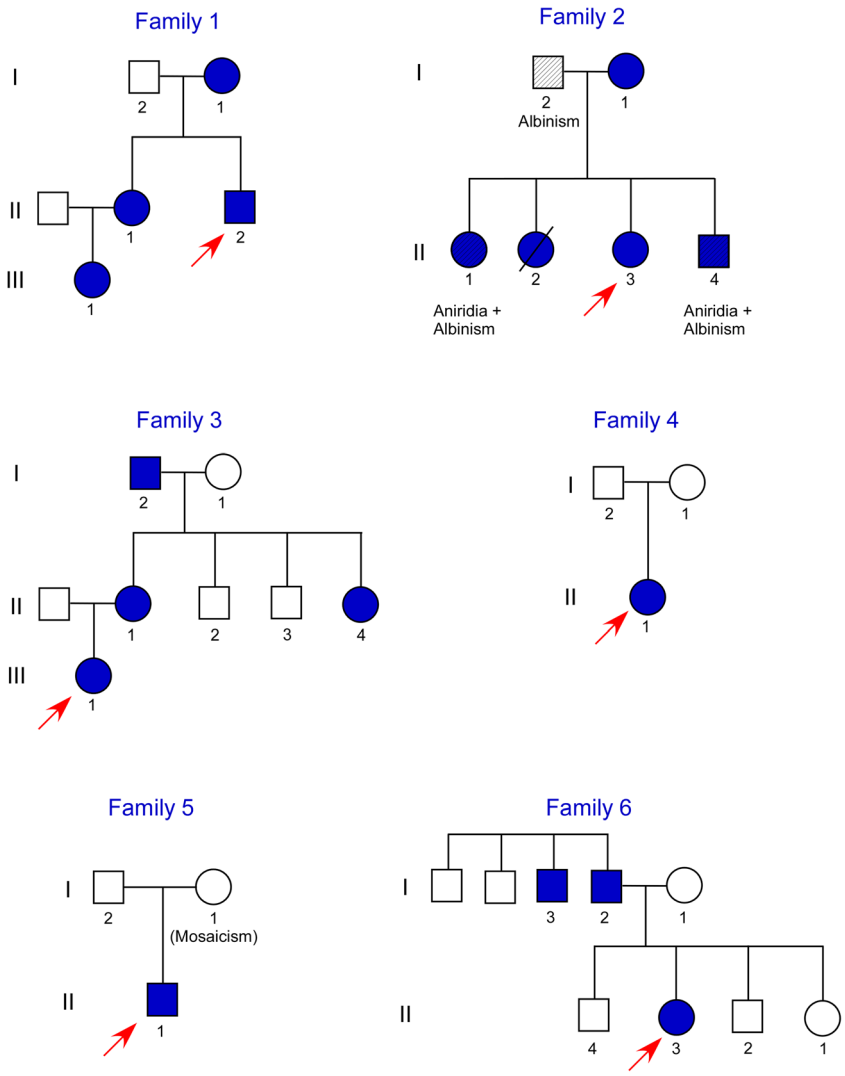

Fig. 3 Pedigree of the studied families. Filled shapes represent affected subjects. Index cases are indicated by red arrow. Deceased objects are shown by a diagonal line

mutation, c.383G>A (p.(Arg128His)), that was predicted to be pathogenic based on bioinformatics (Table 2).

Discussion

In mild or atypical aniridia cases, the entire iris can be present but with mild changes such as an eccentric or misshapen pupil or a minor transillumination defect [4–7]. Therefore, the diagnosis of aniridia can be easily overlooked or delayed [12]. Although this mild phenotype seems to have less severe visual implications compared to "typical" aniridia, these patients still present with a potentially blinding disease that can be inherited by their children. The first family with this mild phenotype was identified in 2013. Since then, with a higher grade of awareness, we have diagnosed an additional five families with similar findings and diagnosis untill 2017. This number probably indicates that this is not a rare diagnosis in patients suffering from low vision. For comparison, during the same period of time we identified eight families with full blown aniridia.

To the best of our knowledge, we describe the largest series of patients with a subtle aniridia phenotype with a confirmed *PAX6* gene mutation. Four families (1, 2, 3, and 6) had two or three generations of family members with undiagnosed atypical aniridia. The iris findings in the studied patients varied from a slight coloboma to mild corectopia. Moreover, corneal peripheral vascularization was observed in 9 out of 11 patients; the remaining two patients were children aged 2 and 3 years old; we can therefore infer that keratopathy will likely develop as these patients age.

In family 1, the index case (II:2) had relatively good vision and no nystagmus; in contrast, his niece (III:1) presented with nystagmus and low vision, indicating phenotypic variability even among members of the same family reflecting diverse expressivity of autosomal dominant disease. Phenotypic variability among patients with *PAX6* mutations has been reported previously [6, 14–17]. For example, Sharan et al. [15] reported

a family with phenotypes that ranged from mild iris abnormalities in some patients to classic aniridia in one child. In addition, De Becker et al. [16] reported seven patients in two families harboring the same point mutation (p.A1630T) in the *PAX6* gene and variable degrees of aniridia. In five of the six studied families a missense mutation in *PAX6* was identified. As reported previously, missense mutations are generally associated with an atypical, relatively mild, form of aniridia [4, 5, 12]. However, nonsense mutations were also associated with variable iris abnormalities including subtle aniridia as described by Sale et al. [18] similar to our findings in family 2. Furthermore, all six families harbor mutations within the conventional 128-residue paired domain of *PAX6*, a finding that may point to a possible genotype-phenotype correlation. Interestingly, most published missense mutations are concentrated at the paired domain (HGMD: www.hgmd.cf.ac.uk).

Different mutations affecting the same codon in the paired domain of the *PAX6* gene generally result in mild phenotypes. Bredrup et al. [19] described a Norwegian family with (p.Arg128Pro) mutation suffering from slight corectopia and foveal hypoplasia. Azuma et al. [20] described four family members harboring another mutation in the same codon (p.Arg128Cys), presented with minimal corectopia and foveal hypoplasia. Heyningen and Williamson [21] described three affected family members in two generations, all with isolated foveal hypoplasia and apparently no iris malformations due to the same (p.Arg128Cys) mutation. In our study, in family 6, the index case also had mild corectopia, foveal hypoplasia and fine peripheral corneal neovascularization, resulting from a novel mutation at the same codon (p.(Arg128His)).

Hanson et al. [12] described affected father and daughter harboring a mutation in (p.Ala33Pro) with partial aniridia. Our patients in family 1, which harbor the same mutation have subtle iris malformations. In addition, affected members in family 2 had c.233_241del (p.(Val78_Pro81delinsAla)) mutation and presented with minor iris changes and fine corneal neovascularization. A missense mutation in the same codon (p.(Val78Gly)) caused mainly foveal hypoplasia in four patients from family 3.

The overall refractive profile of the subjects in this series (Table 1) shows high myopia but some of them have high hypermetropia. This fact was already noticed by Hewitt et al [22]. We believe high refractive errors in these patients is consistent with emmetropization being impaired as is known to occur in other inherited eye diseases causing low vision since early childhood.

In conclusion, we suggest that the term aniridia should be used more extensively than its literal meaning of simply "absence of iris." Of note, aniridia is defined in the last version of ICD-11as a congenital complete or partial absence of the iris, which can be isolate or syndromic, meaning that subtle iris abnormalities are included in the definition of aniridia. Hence, increased awareness of the mild clinical form of aniridia is needed among ophthalmologists, particularly given that subtle forms of aniridia are often misdiagnosed or missed entirely. Our analysis revealed three novel *PAX6* mutations in addition to the wide range of previously reported mutations, providing further evidence of phenotypic heterogeneity with respect to aniridic ocular malformation. The location of the identified mutations within the paired domain of PAX6 seems to correlate with the mild phenotypic characteristics. Accurate diagnosis of the varied phenotype of aniridia can improve clinical care of patients and facilitate genetic testing and counseling for affected families.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study (retrospective), formal consent is not required.

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