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Sir,

A [c.566-2A > G] heterozygous mutation in the *PAX6* gene causes aniridia with mild visual impairment

Aniridia is an autosomal dominant eye disorder caused by *PAX6* gene mutations.[1,2] The disease is characterized by congenital absence of the iris with significant loss of vision due to foveal hypoplasia.[3] Here we report a case, in which a rare *PAX6* mutation causes aniridia with mild visual impairment.

Case report

A 4-month-old female without family history of ocular disorder was referred to our hospital for dilated pupils with photophobia. The parents noticed saccadic eye movements that were prominent in the first weeks of life and tended to decrease gradually. The ophthalmological examination, conducted in a quiet and cooperative child, was carried out without anaesthesia. Slit lamp observation showed bilateral iris hypoplasia with clear corneas and lenses. A horizontal nystagmus of low amplitude was noticed and binocular visual acuity, assessed using Teller acuity cards, was estimated to be 3/60. Intraocular pressure, obtained using a Perkins tonometer, was 8 mm Hg in both the eyes. The fundus examination did identify neither optic nerve abnormality nor foveal hypoplasia, but macular observation was difficult to perform because of nystagmus. At this time, a diagnosis of sporadic aniridia was established, and a mutation analysis of *PAX6* was carried out. The genetic study revealed a heterozygous mutation [c.566-2A > G] in *PAX6* intron 8–9 (http://www.ensembl.org, ENSG00000007372, ENST00000416339, ENSP00000405776) consisting in a splice site defect predicted to hamper proper splicing of the mRNA. None of the two unaffected parents carried this mutation. The patient was kept under review at 3-monthly intervals. Clinical follow-up revealed no dysmorphic features or psychomotor delay. On last examination, at the age of 2 years, the anterior segment presentation remained unchanged (Figure 1). Surprisingly, the nystagmus had completely disappeared and the best-corrected visual acuity, assessed using Teller acuity cards at the age of 18 months, increased to reach 6/18 in each eye. Cycloplegic refraction was $-3.00/+1.25\times165^{\circ}$ (right) and $-2.00/+1.25\times20^{\circ}$ (left). The eye fundus, obtained more easily because of disappearance of nystagmus, appeared to be normal without identifiable foveal hypoplasia.

Comment

Due to early expression in the developing eye, the *PAX6* gene is associated with various congenital ocular malformations, including aniridia, Peters' anomaly, keratitis, congenital cataract, optic nerve malformations, and microphthalmia.[1–4] Aniridia is considered as a haploinsufficiency ocular disorder, and is typically associated with *PAX6* nonsense or frameshift mutations introducing a premature termination codon, whereas *PAX6* missense mutations, of which the majority are located in the paired domain and result in impaired DNA binding, lead to non-aniridia phenotypes. The intriguing aspect of our observation lies in the mild degree of visual impairment with complete disappearance of nystagmus. The mutation encountered here has been reported only twice in human.[4,5] In the first case, the patient harbouring the mutation presented with aniridia, cataract, nystagmus, and corneal dystrophy.[4] In the second case, the mutation was associated with complete iris defect, nystagmus, cataract, and strabismus.[5] Although both phenotype descriptions claims for the presence of cataract and nystagmus, macular hypoplasia was not reported. At present, it is difficult to explain why such a *PAX6* mutation consisting in a splice defect may cause variable clinical presentation with a possible relative preservation of the visual function. A possible explanation is that the predicted existence of an in frame cryptic splice site inside exon 9 or a variation in exon 9 skipping level could lead to a shortened protein partly deprived of transactivation domain instead of full haploinsufficiency.

Conflict of interest

The authors declare no conflict of interest.

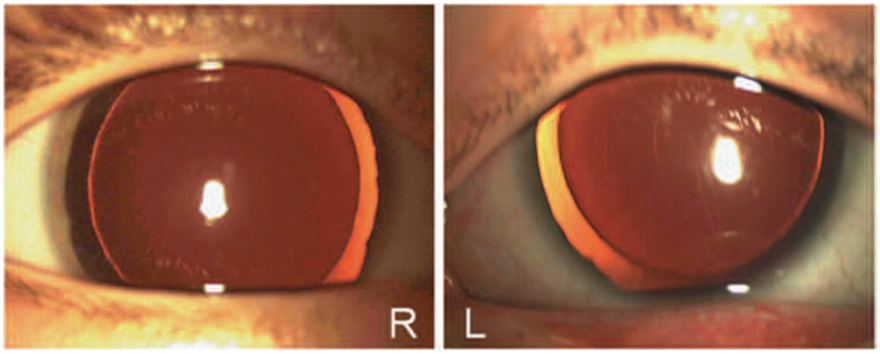

Figure 1 Anterior segment aspect observed in the 2-years-old patient carrying the [c.566-2A > G] mutation in the *PAX6* gene. Slit-lamp biomicroscopy of right eye (R) and left eye (L) showing pronounced iris hypoplasia with clear corneas and complete absence of lens opacities.

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Sir,

Training in trabeculectomy

I read with interest the clinical study of Welch *et al*.[1]

The study highlights the fact that with a decrease in glaucoma surgery trainees have less opportunity for gaining experience in trabeculectomy.

I have worked in West Africa for over 20 years and am the medical director of a 62-bed eye hospital in the north of Benin. In 2010 over 3500 eye surgeries were performed, of which 395 were trabeculectomies.

Open-angle glaucoma is common and is a major cause of blindness. The potent anti-glaucoma medications used in the United Kingdom are too expensive for our poor patients or are unavailable. In any case, many of the glaucoma patients we see have intraocular pressures of 50 or 60 mm Hg and would not respond sufficiently to eye drops however potent. Hence, surgery is the only practical solution.

One possibility for glaucoma surgery training would be for a partnership between hospitals in the United Kingdom and eye hospitals in West Africa, 'the glaucoma capital of the world'. We have the patients. UK consultants and their trainees would be welcome here for short periods.

Conflict of interest

The author declares no conflict of interest.

Reference

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Sir,

One-year results of intravitreal bevacizumab as an adjunct to trabeculectomy for neovascular glaucoma in eyes with previous vitrectomy

Neovascular glaucoma (NVG) is refractory to conventional surgeries including trabeculectomy with mitomycin C (TMMC).[1] Previous vitrectomy, in particular, can adversely affect the outcomes of subsequent TMMC.[1,2] Several studies have reported that bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) can control neovascular activity in eyes with NVG.[3–5] We conducted a pilot study to evaluate the efficacy of intravitreal bevacizumab (IVB) as a preoperative adjunct for primary TMMC to treat NVG in previously vitrectomised eyes.

A total of 15 eyes of 15 consecutive patients (10 men, 5 women) who had undergone a previous vitrectomy received IVB (1 mg) followed by planned TMMC. All patients were followed for more than 1 year postoperatively. The mean patient age was 58.3 ± 11.3 years (31–71 years). NVG was secondary to proliferative diabetic retinopathy in 11 eyes (73%), ocular ischaemic syndrome in 3 eyes (20%), and central retinal vein occlusion in 1 eye (7%). A total of 11 eyes had one, 2 eyes had two, and 2 eyes had three previous vitrectomies. The interval between IVB and TMMC was 10.0 ± 6.4 days (1–22 days). All patient data are shown in Table 1.

The mean intraocular pressure (IOP) reduced significantly from 41.3 ± 11.9 mm Hg (25–62 mm Hg) at baseline to 13.6 ± 7.0 mm Hg (4–32 mm Hg, $P<0.001$, one-way ANOVA followed by Tukey's test) at 1 month, 13.9 ± 4.5 mm Hg (6–18 mm Hg, $P<0.001$) at 3 months, 15.3 ± 5.1 mm Hg (8–23 mm Hg, $P<0.001$) at 6 months, and 15.4 ± 5.2 mm Hg (4–25 mm Hg, $P<0.001$) at 1 year postoperatively. The success rates defined as IOP below 21 mm Hg without loss of light perception and additional anti-glaucoma surgeries were 87% after 1 and 3 months of follow-up, 80% after 6 months, and 73% after 1 year (Figure 1). Failure (four eyes, 27%) was attributed to the additional glaucoma surgery in three eyes and an IOP over 21 mm Hg in one eye.