Newly identified paired box 6 mutation of variant familial aniridia: Congenital iris ectropion with foveal hypoplasia

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Congenital aniridia is a kind of eye disease characterized by complete or partial hypoplasia of the iris and is associated with other ocular anomalies including corneal opacity, glaucoma, and foveal hypoplasia. Heterozygous mutation of paired box 6 (PAX6) gene was identified in most cases of aniridia, with iatrogenic mutations accounting for about two-third of the cases and chromosomal rearrangements accounting for the other one-third. We report rare cases of variant aniridia, congenital iris ectropion associated with foveal hypoplasia in both a woman and her son with a mutation of PAX6 gene. To our knowledge, deletion c. 936delC in exon 8 of PAX6 gene has not been reported until now.

Key words: Congenital iris ectropion, foveal hypoplasia, paired box 6, variant aniridia

Congenital iris ectropion (CIE) is a recently classified disease, added to the spectrum of neural-crest-derived anterior segment dysgenesis syndrome.[1] The posterior pigment epithelium of the iris extends onto the anterior iris surface causing a nonprogressive ectropion of the iris pigment epithelium, a smooth cryptless iris surface. Foveal hypoplasia (OMIM*136520) is an underdeveloped condition and has characteristic morphologic findings such as an absence of foveal pigmentation and foveal avascular zone, and is associated with aniridia and ocular albinism, or may occur as an isolated form.[2] We report a woman and her son with CIE combined with foveal hypoplasia and a mutation in the paired box 6 (PAX6) (OMIM*607108) gene.

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Case Report

A 37-year-old woman with diabetes mellitus visited the clinic to screen for retinopathy complaining poor vision. She underwent a bilateral cataract extraction surgery about 13 years ago. She was normal in growth and did not display intellectual disability. She had two children. Her best-corrected visual acuity was 20/100 in both eyes. Intraocular pressures were normal. Examination of biomicroscopy showed bilateral CIE with clear cornea [Fig. 1a and d]. Fundoscopic examination showed bilateral foveal hypoplasia without other findings of diabetic retinopathy [Fig. 1b, c, e and f]. She had normal cutaneous pigment, absence of ptosis, and nystagmus.

Her first child, 9-year-old son was recruited for clinical test. He has been visiting our clinic for bilateral congenital cataract and ptosis. His best-corrected visual acuity was 20/40 in both eyes. Intraocular pressures were normal. He also had bilateral CIE with clear cornea [Fig. 1g and i]. Fundoscopic examination also showed bilateral foveal hypoplasia [Fig. 1h and j].

With ethics approval and informed consent, an examination for mutation of PAX6 gene on 11p13 chromosome was performed from their blood. The PAX6 coding exons were screened for mutation by sequence analysis and compared with reference sequences in the National Center for Biotechnology Information reference sequence database (http://www.ncbi.nlm.nih.gov/nuccore/NG_008679.1?from=5001andto=38170andreport=genbank).

A deletion of cytosine was detected at nucleotide 936 of the complementary DNA (cDNA) of exon 8 (c.936delC) as a heterozygous form. This mutation causes frameshift of protein 312 (p.G312fs). The mutation was present as a heterozygous form in both the woman and her son [Fig. 2a and b]. The status of father was normal in ocular examination. There were two children; the first child was in our case history and the other was normal in ocular examination. Cosegregation analysis in our cases demonstrated the autosomal dominant mode of inheritance of disease with complete penetrance.

Discussion

PAX6 is known to have a "master role" in eye development. In humans, it is located in chromosome 11p13 and is a well-known gene causing aniridia (OMIM*106210) disease that contains 14 exons and encodes a protein of 422 amino acids. Its mutation leads to a variety of hereditary ocular malformations of the anterior and posterior segment.[3] Aniridia is a congenital, bilateral panocular disease characterized by complete or partial absence of the iris associated with other ocular abnormalities

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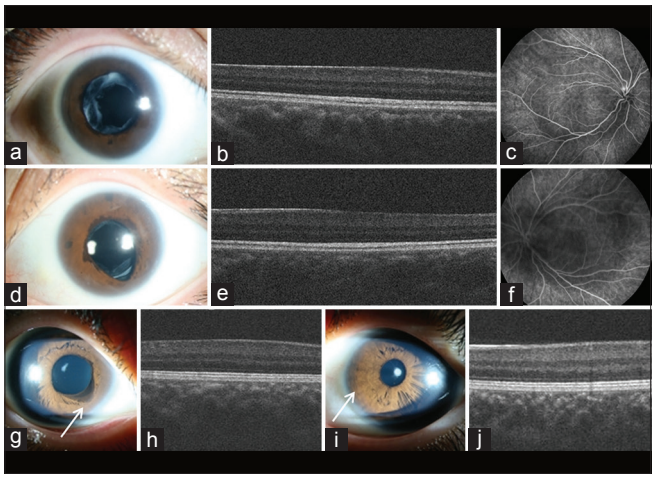

Figure 1: Right eye of the woman with circumferential iris ectropion (a), foveal hypoplasia (b), and absence of foveal avascular zone in fluorescein angiography (c). Left eye of the woman with circumferential iris ectropion (d), foveal hypoplasia (e), and absence of foveal avascular zone in fluorescein angiography (f). Right eye of her son with focal iris ectropion on inferonasal area (arrow) (g), foveal hypoplasia (h). Left eye of her son with a smooth cryptless iris surface on nasal area (arrow) (i), foveal hypoplasia (j)

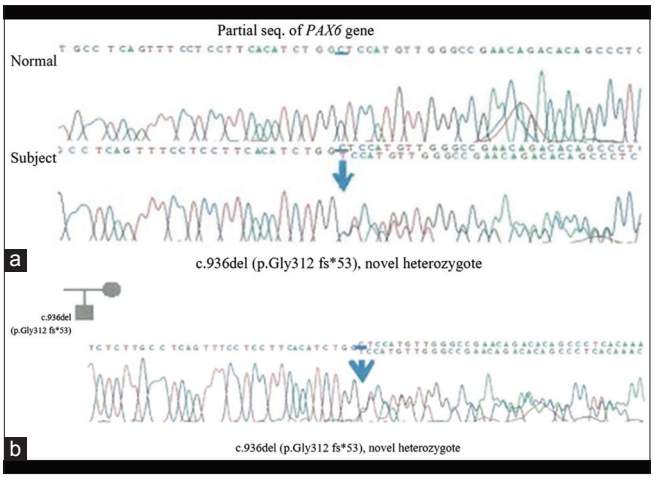

Figure 2: A deletion at nucleotide 936 of the complementary DNA of exon 8 (c.936del). This mutation causes frameshift of protein 312 (p.G312fs). The mutation was present in both her son (a) and the woman (b)

including corneal pannus, cataract, glaucoma, optic nerve hypoplasia, and foveal hypoplasia. CIE is a developmental arrest of neural crest structure and considered as an indicator of variant aniridia.[4] The rare association of CIE with foveal hypoplasia has been previously reported in a pedigree with autosomal dominant transmission.[4] A patient with X423L PAX6 mutation who had bilateral CIE and foveal hypoplasia and a patient with Q422R PAX6 mutation who had CIE and corneal pannus without foveal hypoplasia were reported, previously.[4,5]

Although initial visual acuity in individuals with aniridia may be low due to foveal hypoplasia, progressive visual function loss may occur because of cataract, glaucoma, and keratopathy progression. In our case, the woman had cataract extraction surgery in both eyes. The woman and her son need regular ophthalmologic examination to screen for glaucoma and keratopathy progression.

Heterozygous loss of function of PAX6 as in our cases was identified in about 90% of aniridia cases. Aniridia is dominantly inherited with high penetrance. Affected individuals have a 50% chance of passing the mutant allele to offspring. About one-third of sporadic aniridia cases have a deletion of the Wilms' tumor 1 (WT1) and PAX6 genes and half of these will develop WT.[6,7] This emphasizes the importance of performing genetic analysis in a patient with aniridia.

Until now, approximately 433 DNA mutations have been documented in the PAX6 mutation database (http://pax 6.hgu.mrc.ac.uk/about/pax 6cdna.htm). To our knowledge, a deletion of cytosine at nucleotide 936 of the cDNA of exon 8 is the first reported mutation in PAX6 gene.

In conclusion, if the CIE is bilateral and associated with foveal hypoplasia, the possibility of variant aniridia with a PAX6 gene mutation should be considered. Moreover, genetic consultation is therefore desirable.

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Conflicts of interest

There are no conflicts of interest.

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