# A rare association of aniridia with conjunctival xerosis in two Indian siblings with PAX6 mutation

Dear Editor,

*PAX6* encodes a paired homeodomain transcription factor that plays a vital role in eye and neural development. Its expression is initially found in the anterior neural plate and later on in the lens field of the head surface ectoderm and optic pit.[1] *PAX6* heterozygous gene mutations have been known to cause aniridia, while homozygous mutation is associated with severe brain abnormalities, microencephaly, and early postnatal death with the absence of eye and nose in humans and rodents.[2,3] In the present study, we screened mutation in *PAX6* gene in an Indian family with aniridia and a broad range of ocular malformations.

The case described here is a one and half year old baby girl having multiple ocular complications including bilateral aniridia, microcornea, glaucoma, subluxated lens with no evidence of cataract, high myopia, and conjunctival xerosis [Fig. 1a]. After obtaining the history of patient, a comprehensive ophthalmic examination of anterior and posterior segments was performed. The pupils were dilated using a combination drop of 0.2% cyclopentolate with 1% phenylephrine (Cyclomydril) approximately 15 min before examination. A few examinations were performed under general anesthesia where non-compliance of patient was expected. Visual acuity was evaluated using Teller's acuity card test[4] at a distance of 55 cm. Refraction was performed using cycloplegic retinoscopy. Cover test was performed to assess the binocular vision and ocular motility. Mean intraocular pressure (IOP) was measured with hand-held Perkin's applanation tonometer. Red reflex test was performed to evaluate tear film, cornea, aqueous humor, lens, and vitreous humor. The patient had visual acuity of 26 cycle/degree equivalent to 20/24 of Snellen's Scale in both eyes. The mean refractive error was –4.00 diopters (D) in both eyes, and mean horizontal corneal diameter was 7.5 mm and 8.0 mm in the right and left eyes, respectively. The axial length of right and left eyes were 26.55 mm and 27.24 mm, respectively. Mean intraocular pressure (IOP) was 24 mm Hg in both eyes. The optic cup/disc ratio was not measured and the posterior segment analysis showed myopic fundus.

The patient was prescribed vitamin A (2,00,000 Units) supplementation for the management of conjunctival xerosis till the age of 5 years. Medical records and oral information from the parents revealed that the patient's elder brother also had complex ocular conditions including aniridia, microcornea, glaucoma, subluxated lens, and conjunctival xerosis, while her mother had aniridia and glaucoma, and the father is blind since birth. The family pedigree is shown in Fig. 1b.

Written informed consent was obtained from the parents of the proband. Genetic analysis of the PAX6 gene using polymerase chain reaction and Sanger sequencing was carried out. All the study procedures were conducted in accordance with the tenets of the Declaration of Helsinki and were approved by the Institutional Ethical Committee. Genetic investigations revealed a heterozygous mutation (c.781C>T) in the *PAX6* gene in the patient, her brother, and mother, and not in her father. This mutation is present in exon-10 and was found to cause premature termination of PAX6 protein (p. Arg261Ter) that results in the loss of a partial homeodomain and the entire PST (Proline-Serine-Threonine) domain. *In silico* analyses showed that this mutation is potentially deleterious to the protein function. The PAX6 transcript containing the premature termination mutation (p.Arg261Ter) is believed to undergo nonsense-mediated decay and loss of protein level by 50% that leads to haploinsufficiency and aniridia.[5-7]

Although the *PAX6* mutation (p.Arg261Ter) have been reported in few other population,[8-10] this is the first report from India where this mutation is associated with a broad range of ocular anomalies. To the best of our knowledge, this is the first study to report the association of conjunctival xerosis with aniridia in patients with *PAX6* mutation.

Conjunctival xerosis is a disease associated with vitamin A (retinoic acid) deficiency or insufficiency.[11] A study by Shetti and Patil [1996] showed resolution of Bitot's spot and conjunctival xerosis upon vitamin A supplementation within a month of treatment in a case with aniridia along with conjunctival xerosis and Wilm's tumor.[12] CYP26B1, a retinoic acid metabolizing enzyme is a downstream target of the *PAX6* gene.[13] Therefore; we hypothesize that the presence of conjunctival xerosis in this family with *PAX6* mutation might be owing to the inability of the mutant PAX6 to transactivate Cyp26b1 and subsequent failure in retinoic acid metabolism.

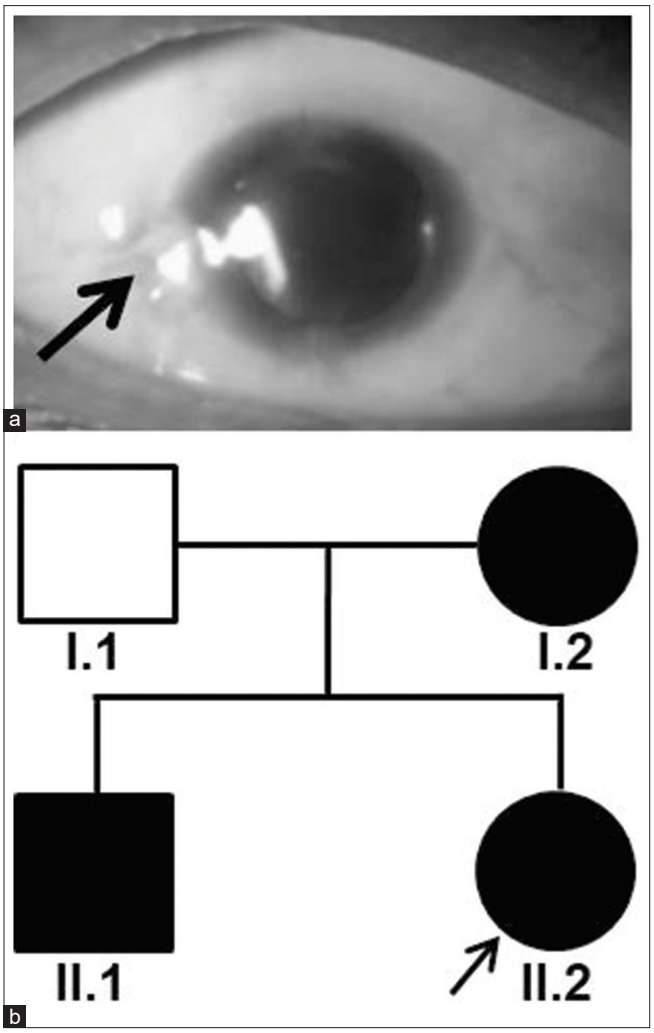


**Figure 1:** (a) Proband's eye phenotype harbouring aniridia, microcornea, glaucoma, subluxated lens and conjunctival xerosis (black arrow). (b) The pedigree chart depicts the affected members (shaded) of the family. The arrow indicates the proband. The father is blind since birth. Except the father, all other members (I.2, II.1 and II.2) carry a heterozygous (c.781C>T) non-sense variation leading to the premature termination (truncation) of PAX6 at amino acid position 261 (p.Arg261Ter)

However, the involvement of other proteins and enzymes responsible for vitamin A binding, transportation, and metabolism could also be considered. Further, *in vitro* and *in vivo* experiments are warranted to confirm this hypothesis.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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