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CASE REPORT

Homozygous variant FOXE3 causes autosomal recessive anterior segment dysgenesis type 2: a case report

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ABSTRACT

Background: Anterior segment dysgenesis (ASD) is a developmental condition that affects the frontal part of the eyes. Genetic mutations in *FORKHEAD BOX E3* can lead to a variety of ASD conditions.

Case Presentation: Here, we report a 2-year-old female patient with ASD type 2 autosomal recessive linked disease. Whole exome sequencing test was conducted and resulted in a missense mutation at position 120 altering arginine to proline. To our knowledge, this is the first case reported in Oman.

Conclusion: For patients with ASD, it is crucial to take the full family history and genetic work up to aid in the diagnosis and long-term management of the condition.

Keywords: Case report, anterior segment dysgenesis, ASD, *FOXE3*.

Background

The anterior segment refers to the front-most region of the eye and includes the cornea, iris, and lens. Anterior segment dysgenesis disorders (ASDs) are a heterogeneous group of developmental conditions affecting this part of the eyes. The features of ASD display extensive phenotypic and genotypic heterogeneity with overlapping clinical features; it includes glaucoma secondary to aqueous humor flow dysregulation from the anterior chamber which can lead to an increase in intraocular pressure (IOP). In addition, features of ASD include iris hypoplasia, an enlarged or reduced corneal diameter, corneal vascularization, and opacity, posterior embryotoxon, corectopia, polycoria, an abnormal iridocorneal angle, ectopia lentis, and anterior synechiae between the iris and posterior corneal surface (1).

ASD has been found to be caused by mutations in genes such as *PXDN (OMIM605158), FORKHEAD BOX E3 (FOXE3) (OMIM601094, NG_016192.1 RefSeqGene), CYP1B1 (OMIM601771), PITX2 (OMIM601542), FOXC1 (OMIM601090), PITX3 (OMIM602669), PAX6 (OMIM607108)*, and *CPAMD8* (*OMIM608841*) which contribute to a spectrum of ocular disorders (2). For instance, *FOXE3*, which is a transcription factor located at chromosome 1p33 and expressed in the lens has a role in the developmental closure of the lens vesicle along with the survival and proliferation of the lens epithelium (3). This gene has been linked with both recessive and dominant eye disease. The recessive mutations in *FOXE3* have been identified in multiple cases with aphakia, microphthalmia, and sclerocornea as major clinical features (4,5). Whereas congenital cataracts and/or anterior segment disease have been seen with the dominant mutations in the same gene (4).

Case Presentation

A 2-year-old girl was referred from Al-Nahdha Hospital (one of the main ophthalmology centers in the Sultanate of Oman) at the age of 7 months for evaluation of aphakia as her sibling has a similar ophthalmological issue.

The child was a term baby, born by spontaneous vaginal delivery with an uneventful postpartum period and normal development. The family history of the child is significant for related parents (consanguineous marriage) (Figure 1), her brother was diagnosed with sclerocornea, anterior segment dysgenesis, and congenital glaucoma

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and was started on treatment. In addition, there was no family history of metabolic diseases.

The child was seen at Al-Nahdha Hospital initially at the age of 40 days when she was referred from a regional hospital for evaluation of white lesions in both eyes. The general physical examination was insignificant with normal skin and no skeletal manifestations. On ophthalmic examination, she was found to have a narrow palpebral fissure, micro-cornea, shallow anterior chamber, and diffuse opacification in both eyes; and IOP was recorded to be 27 mmHg. The child was managed by anti-glaucoma medications at that time, and she was posted for examination under anesthesia (EUA). EUA revealed microphthalmos of the right eye along with sclerocornea, microcornea, and corneal diffuse opacification, and left eye EUA showed corneal diffuse opacification and sclerocornea. The B-scan of both eyes showed aphakia. Cyclophotocoagulation (CPC) was later done for the left eye and was continued on the same anti-glaucoma medications.

When the child was seen at the age of 2 years, parents reported that the child could obey commands, say her name, walk around, and play with other children. She was examined in the clinic, and she was noticed to have white to gray-looking eyes (Figure 2), but dysmorphic features were absent. Additionally, her brother has the same condition and is on the same medications, but he also has esotropia and nystagmus.

Workup

As part of the workup to confirm her suspected condition, a deoxyribonucleic acid (DNA) sample was collected from the child and stored in the Omani National Genetic Center's lab, and whole exome sequencing (WES) was

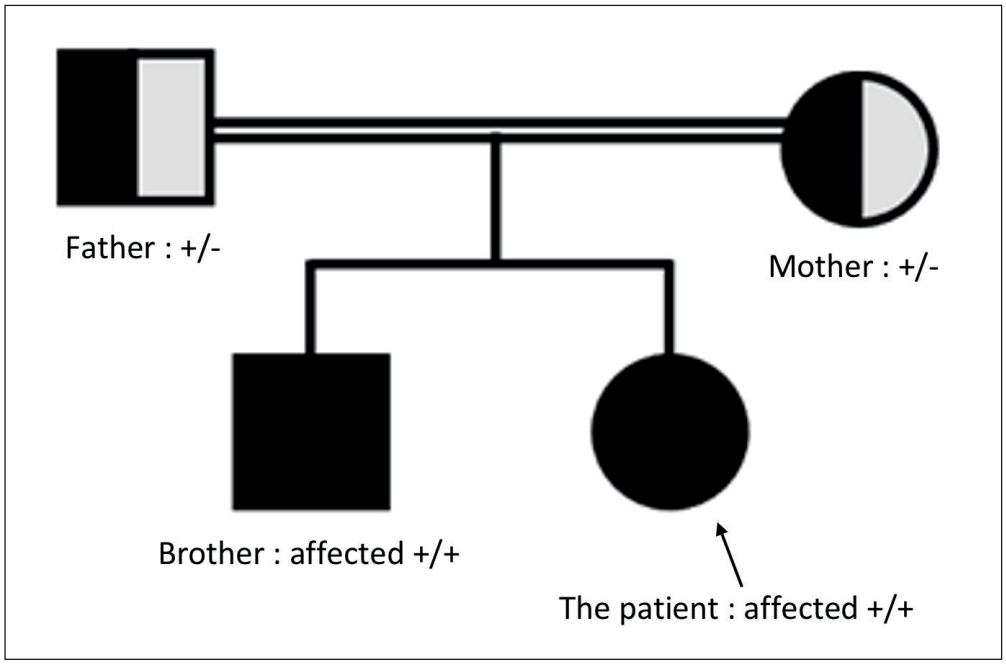

Figure 1. *Family pedigree.*

This figure shows the carrier parent in a consanguineous marriage with affected offspring (male and female).

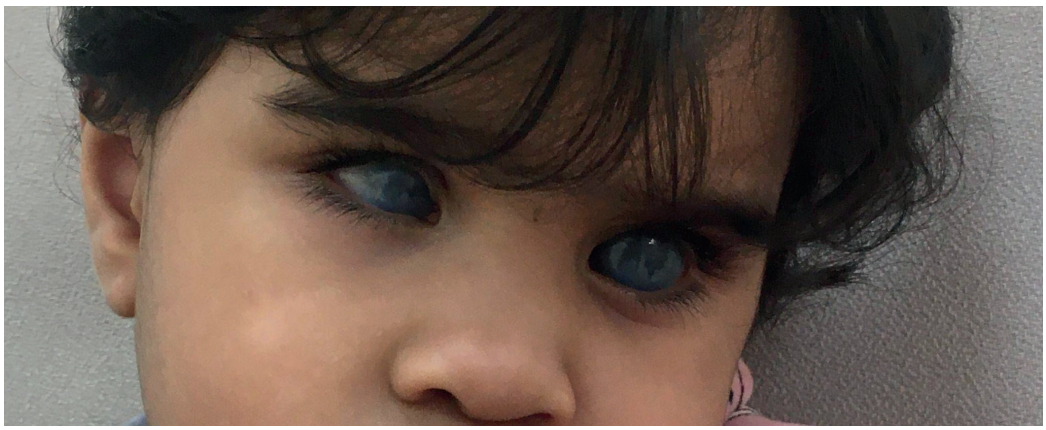

Figure 2. *Clinical features of ASD in the patient.*

This figure displays white lesions in both eyes.

Table. 1. *Comparison of genotype and phenotype between previously reported cases of ASD.*

Publication	FOXE3 Mutation variant	Primary congenital Aphakia	Cataract	Sclero-cornea	Corneal opaci-ties	Megalo-cornea	Glaucoma	Sclero-malacia	Coloboma	Microph-thalmia	Aniridia	Retinal dysplasia
Our case 2022	c.359G>C (Arg-120Pro)	+		+			+					
Chen, 2017 (9)	c.307G>A (p.Glu-103Lys)		+									
Saboo, 2016 (9)	c.472G>C (p.Gl-y158Arg)	+		+						+		
Anjum et al. (5)	c.720C>A (p.Cys240X)	+										
Reis et al. (8)	c.244A>G (p.Met82Val)			+	+		+		+	+		
Iseri et al. (4)	c.244A>G (p.Met82Val)						+	+				
Valleix et al. (7)	c.720C>A (p.Cys240X)	+				+	+			+	+	+

Table 1 shows the differences between the clinical features of our reported case and the previously reported cases.

sent for the same sample. WES revealed the presence of a homozygous variant of uncertain significance class 3 in the *FOXE3* gene (OMIM: 601094) (6) which can possibly explain the phenotype of autosomal recessive ASD type 2.

The WES report also mentioned that the *FOXE3* variant causes an amino acid change from Arg to Pro at position 120. Furthermore, the report listed three conditions that could result secondary to pathogenic variance in this gene; the three conditions are autosomal recessive ASD type 2, autosomal recessive multiple types of cataract type 34, and autosomal dominant susceptibility to familial thoracic aortic aneurysm type 11.

WES was not sent for her brother as he was already known to have the disease; therefore, only a DNA sample was collected, and WES was not requested.

Ethical approval was not required but verbal consent was taken from the parents prior to writing this report.

Discussion

ASD is an umbrella term for a group of disorders affecting the anterior segment of eye development. ASD can be caused by genetic mutations, in our patient, *FOXE3* (*OMIM601094*) was found to be affected at position 120 changing amino acid from arginine to proline (NM_012186: c.359G>C; p. (Arg120Pro); missense with unknown significance).

The patient presented with an opacity of both eyes along with other features – identified by physical examination and EUA – at the age of 40 days and was diagnosed with ASD at the age of 2 years. Similarly, her brother was diagnosed with aphakia, sclerocornea, and congenital glaucoma, however, WES was not carried out for him.

In August 2006, it was first reported that *FOXE3* mutation can cause ocular manifestations; the study included three siblings of a consanguineous family who had features such as microphthalmia and sclerocornea secondary to proven nonsense mutation of *FOXE3* gene inherited in recessive inheritance pattern (7). In 2009, Iseri et al. (4) included two consanguineous pedigrees of Pakistani origin along with two further pedigrees with a total of four families with multiple affected subjects as part of a national developmental eye anomaly study based at Moorfields Eye Hospital, London, and Birmingham Children's Hospital, Birmingham, UK. The manifestations in the four families included anophthalmia, microphthalmia, and coloboma secondary to recessive *FOXE3* mutations identified by whole-genome single-nucleotide polymorphism arrays. In 2010, Reis et al. (8) found that *FOXE3* plays a significant role in autosomal recessive microphthalmia when they included five patients who had manifestations such as microphthalmia, aphakia, and glaucoma secondary to different types of mutations in the *FOXE3* gene; 4 out of the 5 patients belonged to a consanguineous family. And in the same year, Anjum et al. (5) reported a case of congenital primary aphakia inherited in the autosomal recessive manner in a consanguineous Pakistani family secondary to *FOXE3* mutation.

Thirty-three different variants of *FOXE3* mutations were discovered and reported over the past years, 23 of them were missense mutations, and 10 out of the 23 were found to be associated with eye disorders. These ten variants include c.232G>A (p.Ala78Thr), c.244A>G (p.Met82Val), c.269G>T (p.Arg90Leu), c.289A>G (p.Ile97Val), c.292T>C (p.Tyr98His),c.307G>A (p.Glu103Lys), c.310C>T (p.Arg104Cys), c.351C>G (p.Asn117Lys), c.358C>G (p.Arg120Gly), and c.472G>C (p.Gly158Arg) (9). Here, we report a patient with C.359G>C (Arg120Pro) and to our knowledge, this is the first case in Oman of a patient with type II ASD. Additionally, we believe this is the first case with the Arg120Pro missense variant compared to the updated *FOXE3* mutation report published in 2018 (9).

Additionally, the effect of this mutation on protein production was reported to have an unknown significance. However, recent animal studies have revealed the possible damaging effect of missense mutations which renders protein nonfunctional or with low affinity (8,9). Further WES analysis for the patient's brother is recommended to confirm a similar mutation.

As the patient was confirmed to have the condition, it is recommended that she should be followed up regularly with an ophthalmologist to manage her condition. The management will depend on the clinical manifestations of the condition which could involve medications, eye surgery, or corrective lenses for poor vision (10). The patient reported in this study was treated pharmacologically using anti-glaucoma medications and surgically by CPC.

Genetic counseling should be recommended for the family including carrier testing to confirm its hereditary nature. Additionally, pre-natal and pre-implantation diagnosis is necessary to avoid such a disease if the family wishes to get pregnant. This can be accomplished by prenatal genetic testing for monogenetic disorders. The family should be provided with social and emotional support to maintain the child's independence via visual rehabilitation, home assessment, and access to special education.

As the patient is young, we cannot comment on her future outcomes and whether she will develop complicated clinical features like her brother as WES was not carried out for him.

Conclusion

To conclude, ASD is a complex group of disorders that affects patients' vision and development. *FOXE3* gene was found to be affected in our patient resulting in a complex set of symptoms including narrow palpebral fissure, micro-cornea, shallow anterior chamber, and diffuse opacification. For children who are suspected to have ASD, taking a full family history and genetic workup might be necessary to assist in the diagnosis and long-term management of the patient and family.

List of Abbreviations

ASD	Anterior segment dysgenesis
CPC	Cyclophotocoagulation
DNA	Deoxyribonucleic acid

EUA Examination under anesthesia
FOXE3 *FORKHEAD BOX E3*
IOP Intraocular pressure
WES Whole exome sequencing

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The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for publication
Due permission was obtained from the parents of the patient to publish the case and the accompanying images.

Ethical approval
Ethics Approval was granted by Scientific Research Committee, Royal Hospital, Sultanate of Oman, Ministry of Health, via CR#2023/6, dated: 31 January, 2023.

Author contributions
All the authors listed in this article contributed to the acquisition of data from the patient's parents, drafting and writing the manuscript along with final approval of this version to be published.

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