American Journal of Ophthalmology Case Reports 34 (2024) 102060

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Foveal photoreceptor atrophy, persistent fetal vasculature, congenital cataracts, and microphthalmia in a pediatric patient with *BCOR*-associated oculo-facio-cardio-dental (OFCD) syndrome

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A R T I C L E I N F O

Keywords:
BCOR
BCL6 corepressor
Oculo-facio-cardio-dental syndrome
OFCD
Microphthalmia syndromic 2
Persistent fetal vasculature
Microcornea
Congenital cataracts
Foveal photoreceptor atrophy

A B S T R A C T

Purpose: To report a case of oculo-facio-cardio-dental (OFCD) syndrome secondary to a novel *BCOR* variant in a pediatric patient with congenital cataracts, microphthalmia, persistent fetal vasculature (PFV), focal chorioretinal hyperpigmentation, peripheral retinal avascularity, and foveal photoreceptor atrophy.

Observations: A 3-month-old female patient was referred for bilateral congenital cataracts with microphthalmia. Her past medical history was significant for syndactyly of the toes, left bifid rib, atrial septal defect, patent ductus arteriosus, mitral regurgitation, pulmonary hypertension, anemia of prematurity, vesicoureteral reflux, and duodenal atresia. Examination under anesthesia revealed persistent fetal vasculature (PFV) with peripheral avascularity, foveal photoreceptor atrophy, and focal chorioretinal hyperpigmentation. A bilateral lensectomy with anterior vitrectomy and posterior capsulotomy were performed. Genetic testing identified a novel heterozygous pathogenic variant in the *BCOR* gene (c.1612C > T (p.Gln538Ter)), confirming a diagnosis of OFCD syndrome.

Conclusions and importance: This case describes novel posterior segment findings in a patient with OFCD. A detailed examination of both anterior and posterior segments in combination with multimodal imaging should be performed in patients suspected of having OFCD, as this may be critical in determining visual potential and appropriate surgical management.

1. Introduction

Oculo-facio-cardio-dental (OFCD) syndrome is a rare X-linked disorder caused by mutations in the *BCOR* (BCL6 corepressor) gene. Fewer than 100 cases of OFCD have been described and nearly all patients are female, as *BCOR* null mutations are presumed to be lethal in males.[1] OFCD is characterized by microphthalmia, congenital cataracts, secondary glaucoma, canine radiculomegaly, cardiac defects, and digital abnormalities. Typical facial abnormalities include a long and narrow face, high nasal bridge, pointed nose, and cleft palate. Cardiac abnormalities can include atrial septal defect (ASD), ventricular septal defect (VSD), and valvular defects. OFCD was first described by Hayward in 1980 when he observed the co-occurrence of canine radiculomegaly and congenital cataracts.[2] Most cases of OFCD occur due to *de novo* variants, but maternal inheritance has also been reported.[3]

The most common ophthalmic manifestations are congenital cataract and microphthalmia, although anterior segment dysgenesis, secondary glaucoma, coloboma, and anophthalmia have also been reported.[4,5] Regarding vitreoretinal pathology, two patients were previously found to have focal chorioretinal hyperpigmentation, but further retinal characterization by multimodal imaging was not performed.[5,6] We herein report a case of OFCD syndrome with congenital cataracts, microphthalmia, secondary glaucoma, foveal photoreceptor atrophy, focal chorioretinal hyperpigmentation, and persistent fetal vasculature.

2. Case report

A 3-month-old female infant was referred for bilateral congenital cataracts. Her gestation was complicated by polyhydramnios. She was born at 33 weeks gestational age via uncomplicated spontaneous vaginal delivery to a G2P2 mother and required intensive unit (NICU) care for 6 weeks due to meconium staining and prolonged rupture of membranes.

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https://doi.org/10.1016/j.ajoc.2024.102060
Received 6 December 2023; Received in revised form 2 March 2024; Accepted 5 April 2024
Available online 18 April 2024

In the NICU, she received oxygen supplementation for 8 days due to apnea of prematurity and developed disseminated intravascular coagulation (DIC) necessitating infusions of fresh frozen plasma (FFP), cryoprecipitate, and purified red blood cells with platelets. She was noted to have syndactyly of the toes, left bifid rib, atrial septal defect, patent ductus arteriosus, mitral regurgitation, pulmonary hypertension, anemia of prematurity, vesicoureteral reflux, and duodenal atresia. Her ocular family history was only notable for high myopia (-8D) in her father.

Examination under anesthesia (EUA) showed normal intraocular pressures of 14 mmHg in both eyes (OU). Anterior segment examination was notable for microcornea of 7.5 mm, persistent pupillary strands adherent to the anterior lens capsule, as well as anterior capsular (1–2 mm) and central posterior polar cataracts (2–3 mm) OU (Fig. 1). There was no view for a posterior examination. Ultrasound biomicroscopy (UBM) revealed formed anterior chambers with open angles and hyperechoic heterogeneous lens opacities OU (Fig. 1). B-scan ultrasonography showed a thin membrane extending from the optic nerve in the right eye (OD), but no retinal tears, detachments, or masses OU (Fig. 2A). Axial lengths were consistent with microphthalmia (15.56 mm right eye (OD), and 16.27 mm left eye (OS)).[7] A bilateral lensectomy with anterior vitrectomy and posterior capsulotomy was performed. Intra-operatively, a thin posterior stalk of fibrous retrolental tissue was noted OD. Genetic testing utilizing an inherited retinal disorders panel (Invitae Corporation, San Francisco, CA, CLIA-certified) showed no variants. However, a congenital cataract panel (University of Miami Biochemical and Molecular Genetics Diagnostic Laboratory, Congenital Cataract Gene Sequencing Panel, CLIA-certified, all variants confirmed by Sanger sequencing) revealed a novel heterozygous pathogenic nonsense variant in the *BCOR* gene (c.1612C > T (p.Gln538Ter), NM_017745.5) predicted to cause a premature stop codon at codon 538 of the BCOR protein. The DNA position is highly conserved, with a GERP RS score of 5.5999. *In silico* analysis with MutationTaster (www.mutationtaster.org) predicted that the variant is "disease causing" with a probability score of 1. Furthermore, other *BCOR* nonsense variants have been previously described to cause OFCD.[8] After evaluation by a geneticist, the patient was diagnosed with OFCD and then referred to the retina clinic for suspicion of persistent fetal vasculature (PFV).

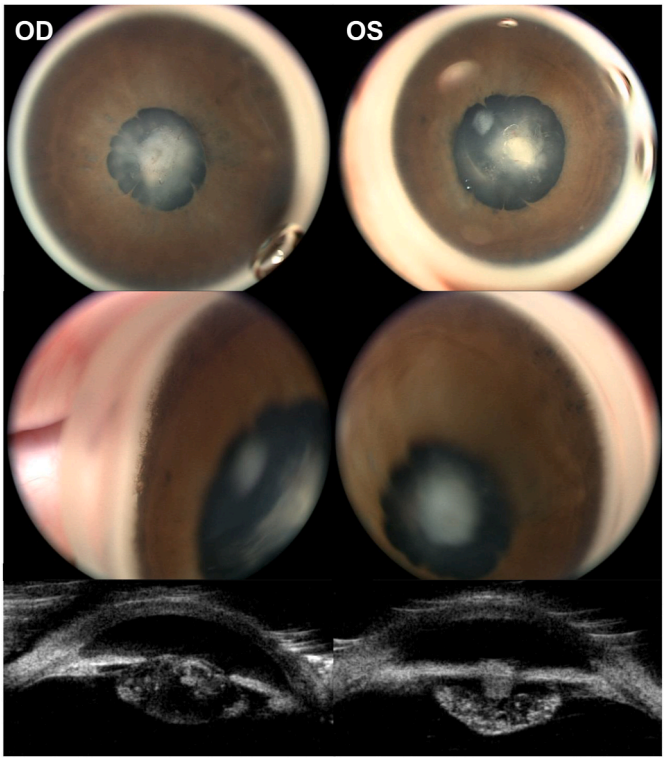

Fig. 1. Anterior segment photos of right (OD) and left (OS) eyes showing anterior capsular and central posterior polar cataracts with persistent pupillary strands attached to the anterior capsule (top row). Gonioscopic photos of right and left eyes show iris processes (middle row). Anterior segment ultrasound biomicroscopy shows formed anterior chambers with hyperechoic heterogenous lens opacities (bottom).

A second EUA was performed at 5 months of age to assess whether the residual stalk of PFV was causing retinal traction OD. Anterior segment examination remained stable and dilated fundus examination revealed sharp disc margins, peripapillary hyperpigmentation, normal foveal reflexes, and abnormal vitreous bases OU (Fig. 2B–D). Photography of the left eye was limited by poor mydriasis. Focal patches of chorioretinal hyperpigmentation were noted in the right eye, mostly inferonasally (Fig. 2D). Intra-operative OCT revealed attenuation and loss of the outer nuclear and ellipsoid zones within the fovea consistent with photoreceptor atrophy OD (Fig. 3A). Fluorescein angiography (FA) showed peripheral non-perfusion OD (Fig. 3B–D). A 27-gauge pars plana vitrectomy (PPV) with synechialysis, capsulectomy, and removal of residual lens material was performed sequentially OU. At 12 months, multi-modal imaging was obtained OS, showing similar focal patches of chorioretinal hyperpigmentation and peripheral non-perfusion (Fig. 4 A-D). However, though there was attenuation of the ellipsoid zone in the macula on OCT, photoreceptors within the fovea appeared to be intact (Fig. 4E). At last follow-up (16 months), the patient was noted to have elevated intraocular pressures of 38 mmHg OD/50 mmHg OS, increased axial lengths (20.9mm OD, 21.8mm OS), partial angle closure due to peripheral anterior synechiae, Haab striae OU, consistent with the development of secondary glaucoma. Topical latanoprost and dorzolamide-timolol were initiated OU, but additional surgery was required for optimal pressure control. Due to the markedly elevated IOP in the left eye (44 mmHg), an Ahmed glaucoma shunt was placed in the ciliary sulcus OS; subsequently, 180° gonioscopy-assisted transluminal trabeculotomy (GATT) with inferonasal goniotomy was performed OD to treat moderately elevated IOP (24 mmHg). At last follow-up, the patient's IOP was 22 mmHg OD and 19 mmHg OS on topical latanoprost and dorzolamide-timolol OU, and her optic nerves were cupped (0.55 OD, 0.45 OS).

3. Discussion

This report describes a case of OFCD associated with novel posterior pathology. While anterior segment abnormalities are more commonly observed in OFCD, posterior segment findings are rare and have been limited to focal chorioretinal hyperpigmentation.[5] This patient also had foveal photoreceptor atrophy and persistent fetal vasculature.

BCOR is a corepressor of BCL6, a POZ/Zinc finger transcription repressor which plays a critical role in the development of the optic cup. It is a ubiquitously expressed nuclear protein involved in the regulation of embryogenesis, mesenchymal stem cell function, hematopoiesis, and lymphoid development.[9] Furthermore, BCOR has been identified as a modulator of photoreceptor gene expression, and some variants in human *BCOR* can lead to early-onset photoreceptor degeneration.[10] Patients with these variants develop an early-onset retinitis pigmentosa and present in their teens or early adulthood with vision loss or nyctalopia despite having no manifestations of OFCD.[10] Although our patient clearly had the systemic manifestations of OFCD, it is possible that her *BCOR* variant also caused photoreceptor atrophy. Further characterization of the phenotypes of specific *BCOR* variants are required. It is likely that female patients will have significant phenotypic variability determined by their specific pattern of X inactivation.

As with foveal atrophy, PFV has also not been described in OFCD, nor has it been attributed to dysfunction of the *BCL6* pathway. PFV occurs when regression of the embryological primary vitreous and hyaloid vasculature fails to occur, and dysregulation of apoptosis has been theorized to be a potential cause.[11] However, the exact pathogenic

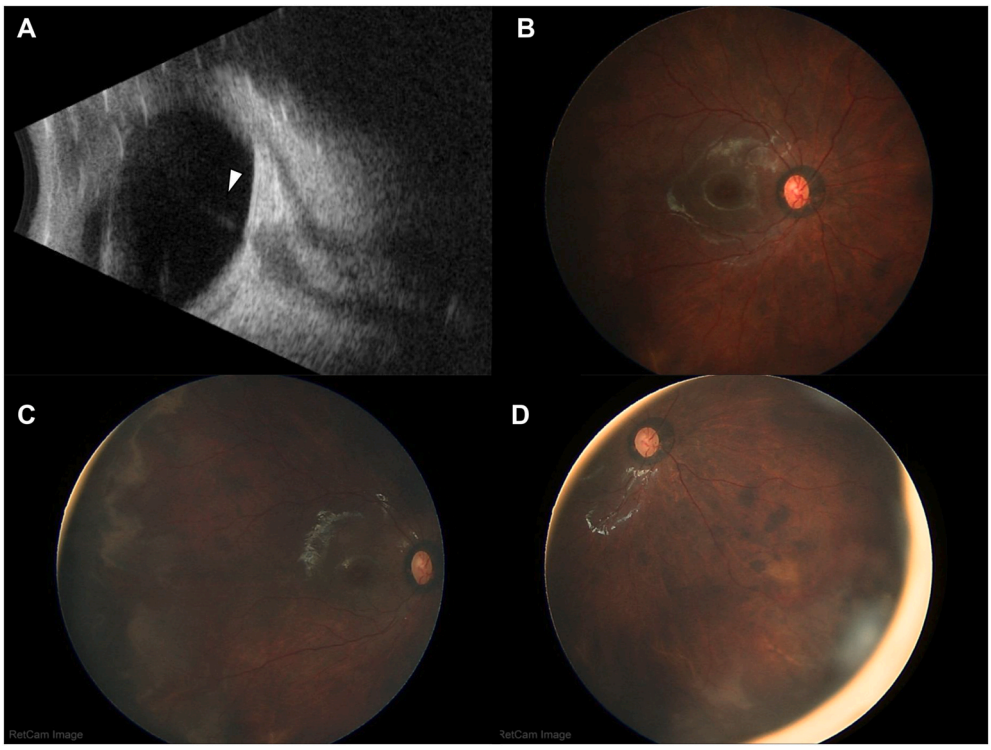

Fig. 2. A. B-scan ultrasonography of the right eye showing a hyperechoic linear stalk extending from the optic nerve consistent with persistent fetal vasculature. B–D: Fundus photographs of the right eye showing focal chorioretinal hyperpigmentation and abnormal vitreous base with incomplete vascularization of the peripheral retina.

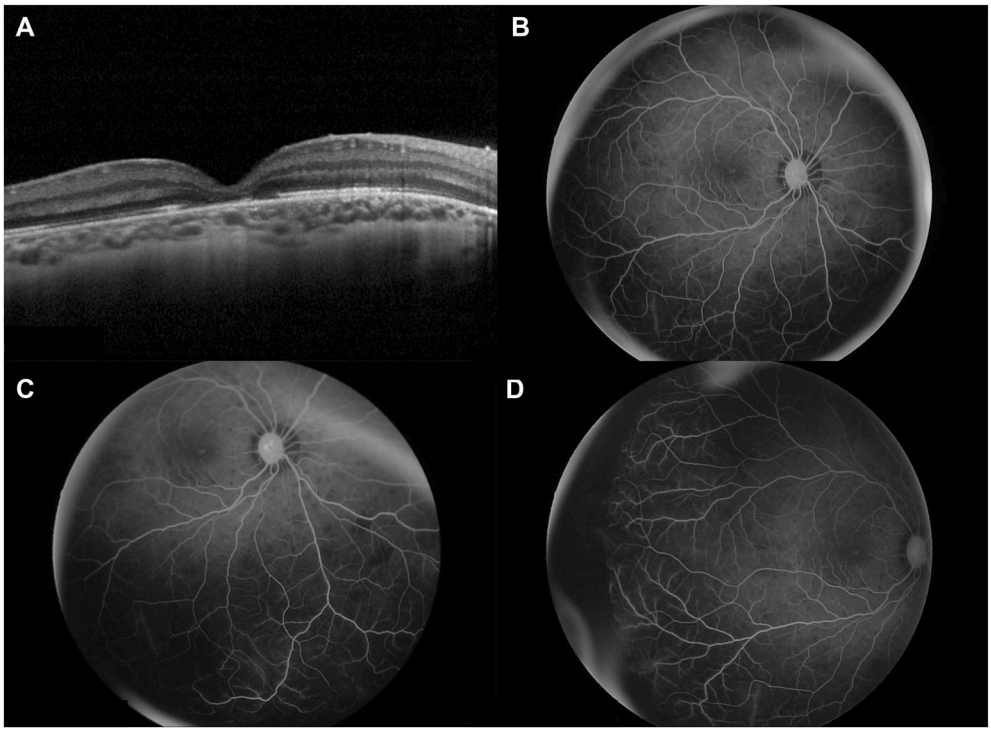

Fig. 3. A. Intra-operative OCT of the right eye showing loss of the outer retinal and photoreceptor layers in the fovea, as well as attenuation of the ellipsoid zone surrounding the fovea. B–D: Intra-operative fluorescein angiography showing the extent of peripheral avascularity in the right eye, as well as blocking of the choroidal flush in the mid-periphery by focal chorioretinal hyperpigmentation.

mechanism remains unclear. In zebrafish, the Bcl6 ortholog Bcl6a has been shown to suppress p53-dependent apoptosis during embryogenesis to prevent formation of colobomata. It is possible that in humans, BCOR and BCL6 also impinge on the apoptosis pathway during embryogenesis, and thus could play a role in regression of the hyaloid artery. However, further studies are required in this area.

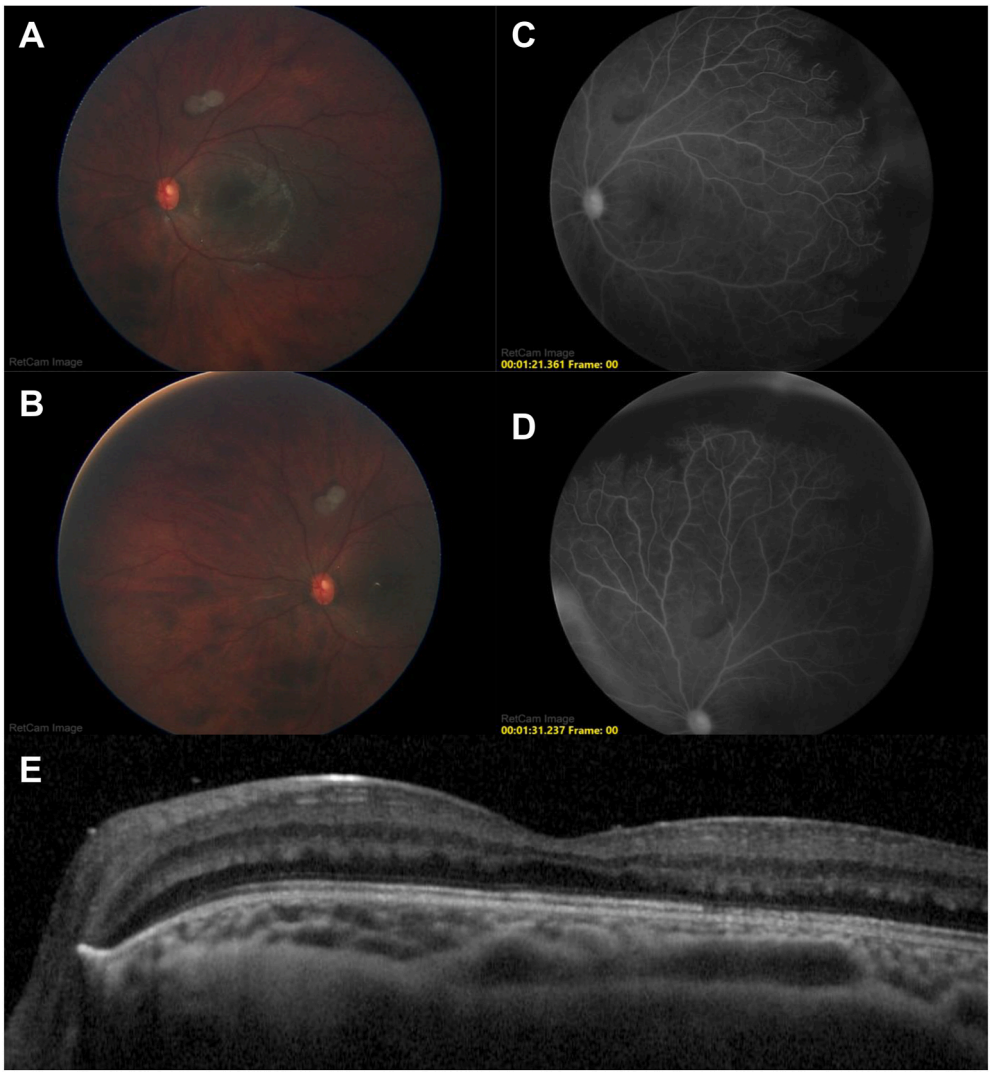

Fig. 4. Multimodal imaging of the left eye. A-B. Fundus photographs showing focal chorioretinal hyperpigmentation similar to the right eye. C-D. Intra-operative fluorescein angiography demonstrating peripheral avascularity. E. OCT macula showing focal ellipsoid zone attenuation without foveal atrophy.

In regard to the peripheral avascularity evident on fluorescein angiography, it is possible that the patient's genetic background, in combination with her prematurity and complicated perinatal course, are contributory. Although she was born beyond the gestational age threshold for retinopathy of prematurity screening, she did have a complicated perinatal course requiring NICU-level care and supplemental oxygen. However, it would be unusual for the avascularity to persist to the age of one year (which is when the last fluorescein angiogram was performed). It is also possible that the bilateral peripheral non-perfusion is associated with persistent fetal vasculature, which has been previously reported.[12,13] However, the degree of non-perfusion in this patient was not asymmetric, which argues against this hypothesis. Whether BCOR dysfunction itself can cause abnormal retinal vascularization remains unknown and requires further study.

In summary, this case demonstrates a novel association between OFCD, foveal photoreceptor atrophy, and persistent fetal vasculature. Management of the better-described anterior segment manifestations of OFCD, such as bilateral cataracts or microphthalmia, should be paired with careful assessment of the retina with multimodal imaging. The presence of PFV or foveal atrophy can significantly impact visual prognosis, counseling of the family, and surgical management in patients with OFCD.

Funding/support

US National Institutes of Health Center Core Grant P30EY014801; an unrestricted grant to the University of Miami from the National Eye Institute; and Research to Prevent Blindness, New York, NY, USA (GR004596-1).

Patient consent

Consent to publish the case report was obtained. This report does not contain any personal information that could lead to the identification of the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Jason Fan: Data curation, Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Natasha Ferreira Santos da Cruz:** Conceptualization, Data curation,

Writing – review & editing. **Catherin I. Negron:** Conceptualization, Data curation, Investigation. **Angela Y. Zhu:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Ta C. Chang:** Investigation, Validation, Writing – review & editing. **Audina M. Berrocal:** Investigation, Writing – original draft, Writing – review & editing, Conceptualization, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank all Bascom Palmer Eye Institute staff involved in the care of this patient.

References

1. Hamline MY, Corcoran CM, Wamstad JA, et al. OFCD syndrome and extraembryonic defects are revealed by conditional mutation of the Polycomb-group repressive complex 1.1 (PRC1.1) gene BCOR. *Dev Biol*. Dec 1 2020;468(1-2):110–132. https://doi.org/10.1016/j.ydbio.2020.06.013.
2. Hayward JR. Cuspid gigantism. *Oral Surg Oral Med Oral Pathol*. Jun 1980;49(6):500–501. https://doi.org/10.1016/0030-4220(80)90070-5.
3. Hedera P, Gorski JL. Oculo-facio-cardio-dental syndrome: skewed X chromosome inactivation in mother and daughter suggest X-linked dominant Inheritance. *Am J Med Genet A*. Dec 15 2003;123A(3):261–266. https://doi.org/10.1002/ajmg.a.20444.
4. Hu Q, Mai J, Xiang Q, Zhou B, Liu S, Wang J. A novel deletion mutation in the BCOR gene is associated with oculo-facio-cardio-dental syndrome: a case report. *BMC Pediatr*. Feb 7 2022;22(1):82. https://doi.org/10.1186/s12887-022-03148-x.
5. Zhou Y, Wojcik A, Sanders VR, Rahmani B, Kurup SP. Ocular findings in a patient with oculofaciocardiodental (OFCD) syndrome and a novel BCOR pathogenic variant. *Int Ophthalmol*. Dec 2018;38(6):2677–2682. https://doi.org/10.1007/s10792-017-0754-5.
6. Mezad-Koursh D, Rosenfeld E, Bachar Zipori A, Zur D, Elhanan E, Ben-Shachar S. A rare genotype of biallelic mosaic variants in BCOR gene causing a bilateral ocular anterior segment dysgenesis and cataracts. *Eur J Hum Genet*. Jan 2023;31(1):125–127. https://doi.org/10.1038/s41431-022-01195-7.
7. Bach A, Villegas VM, Gold AS, Shi W, Murray TG. Axial length development in children. *Int J Ophthalmol*. 2019;12(5):815–819. https://doi.org/10.18240/ijo.2019.05.18.
8. Ng D, Thakker N, Corcoran CM, et al. Oculofaciocardiodental and Lenz microphthalmia syndromes result from distinct classes of mutations in BCOR. *Nat Genet*. Apr 2004;36(4):411–416. https://doi.org/10.1038/ng1321.
9. Sportoletti P, Sorcini D, Falini B. BCOR gene alterations in hematologic diseases. *Blood*. Dec 16 2021;138(24):2455–2468. https://doi.org/10.1182/blood.2021010958.
10. Langouet M, Jolicoeur C, Javed A, et al. Mutations in BCOR, a co-repressor of CRX/OTX2, are associated with early-onset retinal degeneration. *Sci Adv*. Sep 9 2022;8(36), eabh2868. https://doi.org/10.1126/sciadv.abh2868.
11. Thomas DM, Kannabiran C, Balasubramanian D. Identification of Key genes and pathways in persistent hyperplastic primary vitreous of the eye using bioinformatic analysis. *Front Med*. 2021;8, 690594. https://doi.org/10.3389/fmed.2021.690594.
12. Laura DM, Staropoli PC, Patel NA, et al. Widefield fluorescein angiography in the fellow eyes of patients with presumed unilateral persistent fetal vasculature. *Ophthalmol Retina*. Mar 2021;5(3):301–307. https://doi.org/10.1016/j.oret.2020.07.020.
13. Shen JH, Liu L, Wang NK, et al. Fluorescein angiography findings in unilateral persistent fetal vasculature. *Retina*. Mar 2020;40(3):572–580. https://doi.org/10.1097/IAE.0000000000002398.