A Case Report: *BCOR*-related congenital hypertrophy of the retinal pigment epithelium

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PURPOSE

To report a case of *BCOR*-related congenital hypertrophy of the retinal pigment epithelium (CHRPE), which has not been well-documented within the literature.

BACKGROUND

CHRPE is a usually benign hamartoma occurring within the retinal pigment epithelium. While isolated CHRPE can be seen in the general population, bilateral or multifocal CHRPE lesions with an irregular shape are often seen with Familial Attenuated Polyposis (FAP). An association between CHRPE and the *BCOR* gene associated with X-linked Microphthalmia, syndromic 2, a spectrum disorder which includes oculofaciocardiodental (OFCD) syndrome, has been reported in the literature. However, these instances are scant. Here, we describe a patient tested in our laboratory with CHRPE and clinical features suggestive of OFCD that was identified to have a likely pathogenic variant within the *BCOR* gene.

METHODS

The proband, a newborn female, was tested by diagnostic trio whole exome sequencing (WES). The patient's ocular and other systemic findings as well as the pregnancy and family history provided by the clinic were reviewed as part of diagnostic testing. At the time that the patient's results were reported, a literature review for patients previously identified to have CHRPE and a pathogenic finding within the *BCOR* gene was performed (Table 1).

FIGURE 1

Figure 1: A graphic view of pathogenic (red) and likely pathogenic (orange) *BCOR* SNVs and indels documented in ClinVar. Of 54 variants, 34 of them are frameshift variants and 13 are nonsense variants. Only exons 4 through 15 are shown as pathogenic and likely pathogenic variants in exons 1-3 have not been documented in ClinVar.[1]

TABLE 1

Proband Phenotype and Family History	Genetic Testing Performed
Female, age not specified. Fetal history complicated by gestational diabetes, IUGR and multiple congenital anomalies including facial dysmorphism. Heart murmur secondary to ASD and PDA. Right clubfoot, and bilateral 2-3 toe syndactyly. At 5w evaluated for laryngeal cleft type 1. At 5m evaluated for central posterior cortical cataracts, bilateral CHRPE inferior to the optic disk, noted to have epicanthal folds and symmetric blepharoptosis.[2]	Chromosomal microarray (CMA) negative. SLOS biochemical testing indicated normal 7-DHC levels. WES positive for *BCOR* c.3487C>T; p.R1163X variant in exon 7. Parental follow-up was negative.[2]
15 yo female. At 1m bilateral congenital cataracts removed. At 3.5y evaluated for bilateral secondary glaucoma, bilateral inferior multifocal CHRPE with pigmentation adjacent to the optic disk in the right eye and scalp hemangioma. At 8y evaluated for VSD, dental anomalies, flat feet, high-arched palate, and facial dysmorphism. Paternal grandmother had colon polyp at 28y, no known history of *APC* testing.[3]	*APC* mutation testing negative. *BCOR* sequencing positive for c.776C>A; p.S259X variant in exon 4. Parental follow-up declined.[3]
10 yo female. At 1m ASD identified. At 5w bilateral cataracts removed. At 3m evaluated for increased IOP in right eye; hemangioma near right eyebrow, bilateral CHRPE, soft protuberance on parietal scalp and left eye microphthalmia noted. At 11m evaluated for PHACE syndrome due to protuberance. At 9y seen by genetics to confirm PHACE syndrome diagnosis.[3]	*BCOR* sequencing positive for c.2514delG; p.K839Sfs*17 in exon 4. Follow-up testing for parents and sister was negative.[3]

Table 1: Previously reported patients in the literature with CHRPE positive for pathogenic *BCOR* variants.

FIGURE 2

Figure 2: Multiple lesions of CHRPE near the optic nerve (from Morgan et al., see References).

RESULTS

The patient was noted by their clinical team to have bilateral CHRPE by eye exam. Systemic findings include an atrial septal defect, ventricular septal defect, dysplastic pulmonary valve, overlapping toes, cleft palate, pulmonic stenosis, and facial dysmorphism. Pregnancy history positive for polyhydramnios, increased nuchal translucency, and maternal COVID-19 infection. The family history was unremarkable for related findings.

A chromosomal microarray had been performed prenatally and was normal. No findings in the *APC* gene were identified by WES. A heterozygous variant in the *BCOR* gene, c.3635_3638dup, p.L1214Afs*3 in exon 8, was identified by WES in this patient. This variant has not been described in ClinVar or gnomAD nor previously identified internally. Parental follow-up indicated this is a de novo variant. Most SNVs and indels that are pathogenic in *BCOR* are located in exons 4 through 15 and are frameshift variants (Figure 1). Given this information, this variant was classified as likely pathogenic.

CONCLUSIONS

The patient's clinical, prenatal CMA, and WES findings are consistent with OFCD syndrome. To our knowledge, this is the third patient in the literature to have CHRPE and a pathogenic *BCOR* variant that does not have a known *APC* variant. This case report provides additional evidence that *BCOR* molecular testing should be considered for patients with CHRPE findings suggestive of FAP, who have additional phenotypes consistent with a congenital anomaly syndrome.

REFERENCES

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