



## Familial exudative vitreoretinopathy associated with retinal astrocytic hamartoma

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### ABSTRACT

**Purpose:** To report the first case of retinal astrocytic hamartoma (RAH) arising in the setting of Familial Exudative Vitreoretinopathy (FEVR).

**Observations:** An otherwise healthy 3-month-old male was clinically diagnosed with Familial Exudative Vitreoretinopathy, with subsequent confirmation of a Frizzled-4 nonsense gene mutation. He was treated with multiple rounds of laser photocoagulation after demonstrated peripheral non-perfusion on fluorescein angiography. At 4 years of age, he was noted to have a solitary retinal astrocytic hamartoma in an area of anterior retinal traction which remains under observation.

**Conclusions and Importance:** This case describes the first reported instance of a retinal astrocytic hamartoma arising in the setting of FEVR. Multiple factors may have contributed to the formation of this benign tumor, including retinal dysgenesis, genetic background, or even laser photocoagulation. More case reports and/or molecular studies are required to further clarify the potential role of these insults in the pathogenesis of RAH.

### 1. Introduction

The widespread adoption of next-generation sequencing for the diagnosis of inherited retinal diseases has allowed clinicians to characterize unique phenotypes in the setting of rare genetic backgrounds. As novel genetic variants continue to be identified, subtleties in presentation must be reported to optimize clinical management. We herein report the co-occurrence of two rare entities: retinal astrocytic hamartoma (RAH) and Familial Exudative Vitreoretinopathy (FEVR). Retinal astrocytic hamartomas are rare benign tumors arising from the retinal nerve fiber layer composed predominantly of astrocytes.<sup>1–3</sup> They can be associated with systemic phakomatoses (i.e. tuberous sclerosis, neurofibromatosis type 1) or chronic retinal degenerations such as retinitis pigmentosa, but may also be sporadic. Although typically slow-growing, retinal astrocytic hamartomas may cause vitreous hemorrhage, retinal detachment, cystoid macular edema, retinal vein occlusions, or neovascular glaucoma. FEVR may generate an inflammatory milieu conducive to the formation of benign astrocytic proliferation but the coexistence of these two entities has never been reported.

### 2. Case report

A 3-month-old male born at 38 weeks without complication by Caesarean section (birth weight 3969 g) with a family history of familial exudative vitreoretinopathy (FEVR) presented for ophthalmologic assessment. Examination under anesthesia (EUA) was performed and showed an unremarkable anterior exam, bilateral retrolental fibroplasia, and bilateral temporal macular dragging with large retinal folds extending through the macula to the periphery (Fig. 1A–B). No obvious foveae could be identified, and no foveal avascular zone was detected on fluorescein angiography (FA) (Fig. 1C–D). There was also slow venous filling with significant peripheral non-perfusion bilaterally. The patient received laser photocoagulation to the areas of avascularity in both eyes and was clinically diagnosed with FEVR.

Repeat EUA was performed at 5 months of age and showed small pinpoint areas of neovascularization temporally in both eyes (Fig. 2A–D). The decision was made to augment the previous photocoagulation peripherally. At 8 months of age, FA demonstrated mild leakage of the peripheral vasculature in both eyes and additional photocoagulation was once again performed using large spot indirect

; RAH, Retinal Astrocytic Hamartoma; FEVR, Familial Exudative Vitreoretinopathy.

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diode laser.

At 4 years of age, alternating patching was initiated for strabismus with highly variable angle esotropia to exotropia with pseudo-exotropia from strong positive angle kappa in both eyes. EUA performed 4 months later revealed a yellow-white, mulberry-like, astrocytic hamartoma with fine feeder vessels in the right eye (Fig. 3A–E). Of note, the RAH appeared slightly posterior to an area of anterior traction and vitreous condensation that was contiguous with the previously noted retrolental fibroplasia (Fig. 3E). Moreover, FA showed that the RAH had formed a shared vascular network with the retrolental fibrovascular membrane, and that the RAH itself had late staining without leakage (Fig. 3F). The anterior tractional membranes were otherwise noted to be stable in both eyes. A vascularized retinal fold with staining of peripheral fibrosis was seen in the left eye (Fig. 3D). Given clinical quiescence of disease, the decision was made to observe the lesion. Systemic evaluation for tuberous sclerosis and neurofibromatosis type 1 were performed in conjunction with the patient's pediatrician: dermatologic survey, neuroimaging, EEG, CT chest abdomen and pelvis, and renal ultrasound did not reveal findings suggestive of either disease.

At 6 years of age, the patient developed posterior subcapsular cataracts OU, which were not visually significant, as well as bilateral band keratopathy. Repeat renal ultrasound was within normal limits and work-up for hypercalcemia is pending. B-scan ultrasonography OD showed a small hyperechoic focus inferotemporal and posterior to the equator corresponding to the location of the retinal fold rather than the RAH. This hyperechoic focus likely represents early calcification of the retinal fold (Fig. 4).

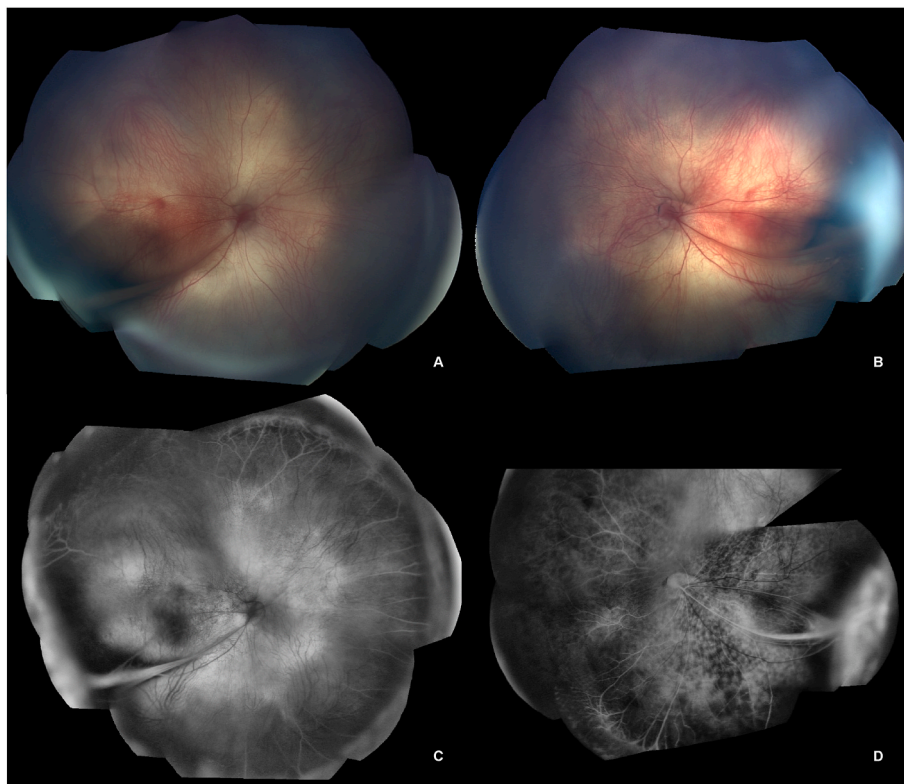
Additional history and examination of family members revealed that the patient's mother and maternal uncle both had peripheral avascularity, and that the patient's mother had zone 3 neovascular fronds. Genetic testing utilizing the Invitae Inherited Retinal Disorders panel was performed (Invitae, San Francisco, CA). A pathogenic variant in the Frizzled-4 gene (FZD4) was identified (c.661dup, p. Ile221Asnfs\*27).

This variant is predicted to result in a premature stop codon leading to disruption of the last 317 amino acids of the FZD4 protein. Notably, other variants disrupting the C-terminus of this protein have also been shown to be pathogenic (p.Trp496\*, p. Gln505\*). Sequencing also revealed that the patient had a variant of unknown significance (VUS) in the USH2A gene (c.6590C>T (p.Thr2197Ile) which is associated with autosomal recessive Usher syndrome 2A and retinitis pigmentosa. Although the mutation is predicted to cause a missense mutation with possible functional effects, its clinical significance has not been confirmed.

### 3. Discussion

This unique case is the first report of an isolated retinal astrocytic hamartoma (RAH) arising in the setting of FEVR. RAH are rare benign retinal tumors arising from the nerve fiber layer that are composed of glial cells, of which astrocytes are the predominant cell type. They typically appear as yellow-gray sessile masses in the posterior pole, and may have intrinsic calcification and vascularity.<sup>1,2</sup> OCT imaging shows a thickened, hyperreflective, dome-shaped tumor within the retinal nerve fiber layer with optically empty ("moth-eaten") spaces likely representing intralaminar cavitation.<sup>3</sup> They can be associated with systemic phakomatoses such as tuberous sclerosis or neurofibromatosis type 1 (NF) but may also be seen sporadically, or in chronic retinal degenerations such as retinitis pigmentosa.<sup>4</sup> Sporadic RAH are typically solitary and unilateral, while those associated with phakomatoses tend to be multifocal and bilateral.<sup>5</sup> To date, the occurrence of RAH has not been reported with FEVR.

FEVR was first described by Criswick and Schepens in 1969 and encompasses a group of inherited retinal disorders characterized by incomplete vascularization of the peripheral retina.<sup>6</sup> Penetrance, laterality, and degree of visual loss can be highly variable, even within the same family. The mode of inheritance may be autosomal dominant,



**Fig. 1.** A, B: Montage of fundus photos of both eyes at the time of diagnosis (3 months of age) showing lightly pigmented fundi with poor foveal contour, retinal vessel straightening, temporal dragging, and retinal folds bilaterally. C, D: Fluorescein angiography of both eyes showing macular dragging with anterior traction, peripheral avascularity with neovascular fronds, and scattered areas of hypofluorescence of the left eye.

recessive, or X-linked recessive, and causative mutations in multiple genes have been identified (FZD4, LRP5, TSPAN12, NDP, ZNF408, and KIF11).<sup>7</sup> Many of these genes play a role in the Wnt signaling pathway, which is required for retinal vascular development.<sup>8</sup> Mutations in FZD4 (such as the one in our patient) are the most common causative variants and are associated with autosomal dominant disease. In FEVR, the ischemic peripheral retina promotes neovascularization, and thus laser photocoagulation is often utilized for the prevention of further complications. The efficacy of anti-VEGF agents in this disease remains to be determined and is an active area of investigation.

In our patient, it is unclear whether his genetic background predisposed him to the development of RAH. He lacked the classic systemic associations of RAH, and no evidence of tuberous sclerosis or NF1 were found on systemic evaluation. Although RAH has been associated with retinitis pigmentosa,<sup>9</sup> the significance of the patient's USH2A mutation remains unclear. Additionally, the patient had a single RAH whereas patients with systemic disease often have bilateral or multifocal RAH. However, RAH may also be the sole presenting feature of tuberous sclerosis and may represent a *forme fruste* of the disease.<sup>10</sup> Finally, astrocyte activation can occur in response to different forms of retinal injury, and the chronic retinal changes seen in FEVR, or even laser photocoagulation, may have created a milieu for astrocytic activation and hamartoma formation.<sup>11</sup> Indeed, the unusual location of this RAH in the periphery as opposed to the posterior pole may be more suggestive of an iatrogenic etiology.

RAH are often indolent and slow-growing, though they may rarely cause vitreous hemorrhage, retinal detachment, cystoid macular edema, retinal vein occlusions, or neovascular glaucoma.<sup>12</sup> Although observation is generally sufficient, aggressive RAH causing complications may be treated with cryotherapy, photodynamic therapy, or laser photocoagulation. Future reports of RAH in rare pediatric retinal diseases may

help in characterizing the pathogenesis, natural history, and proper clinical management of these lesions in unique genetic backgrounds.

#### Patient consent

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

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#### Authorship

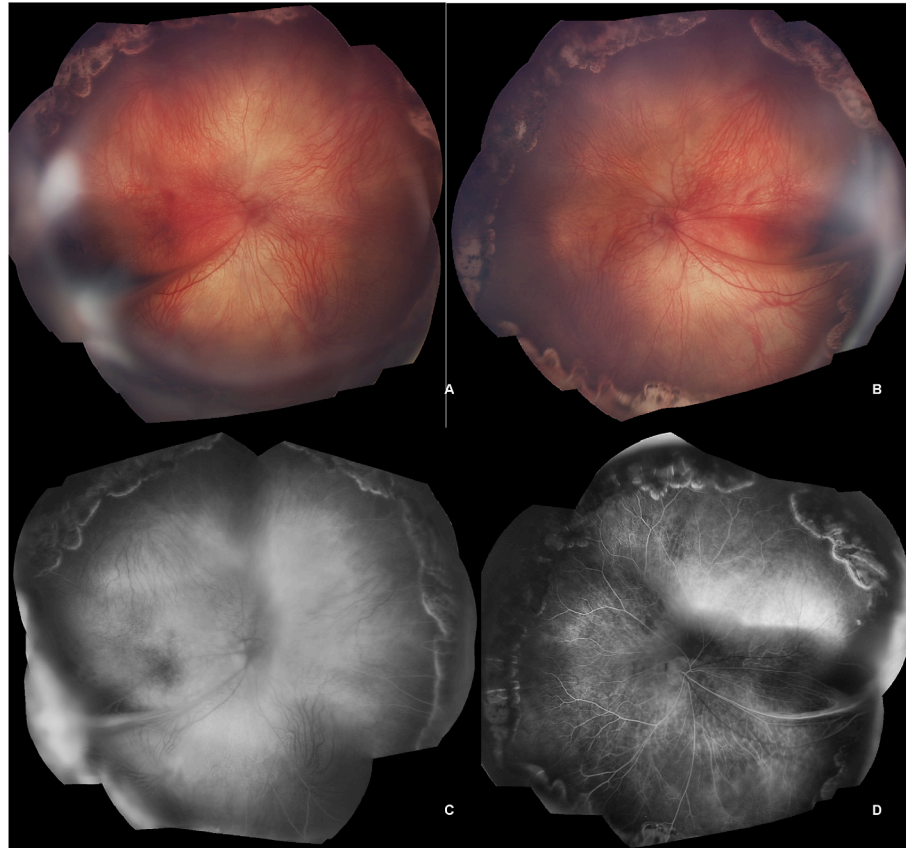
All authors attest that they meet the current ICMJE criteria for Authorship.

#### CRediT authorship contribution statement

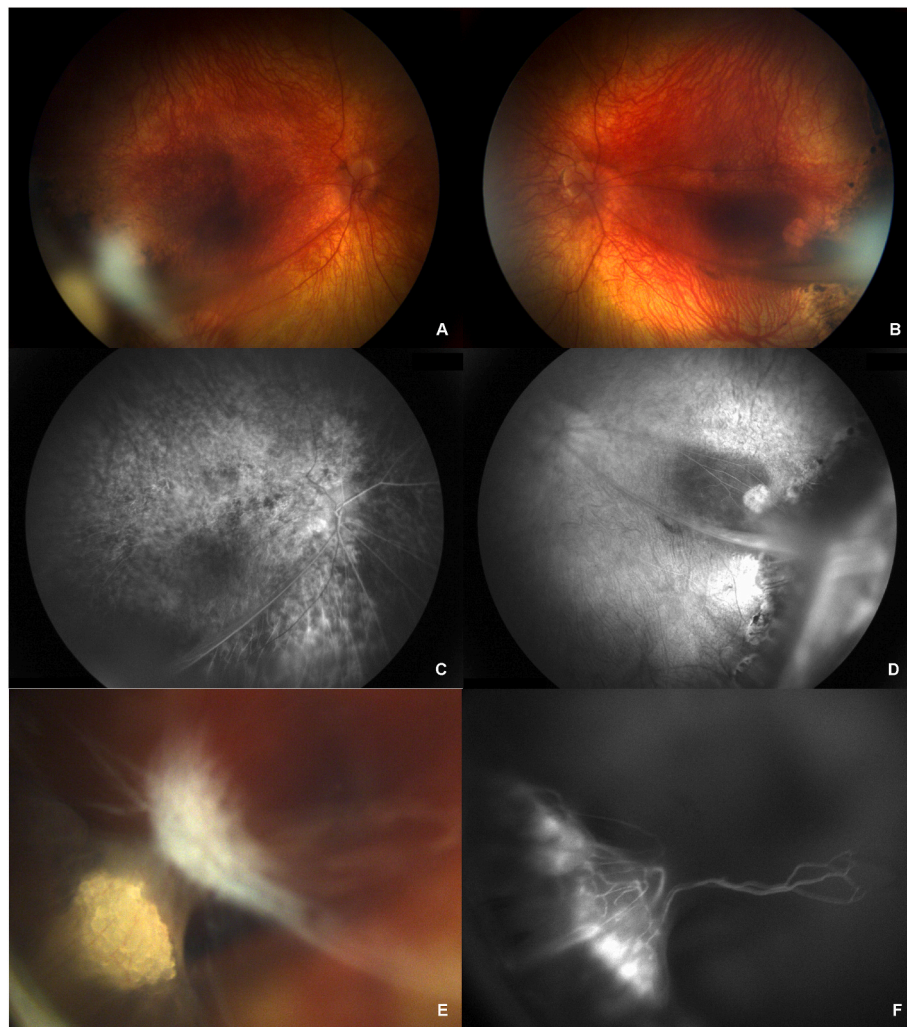
**Jason Fan:** Writing – original draft, Visualization, Writing – review & editing. **Nandini Venkateswaran:** Writing – original draft, Visualization. **Kenneth C. Fan:** Writing – review & editing, Visualization. **Linda A. Cernichiaro:** Conceptualization, Investigation. **Catherin I. Negron:** Conceptualization, Investigation. **Craig A. McKeown:** Conceptualization, Investigation. **Audina M. Berrocal:** Conceptualization, Investigation, Resources, Supervision, Project administration.

#### Declaration of competing interest

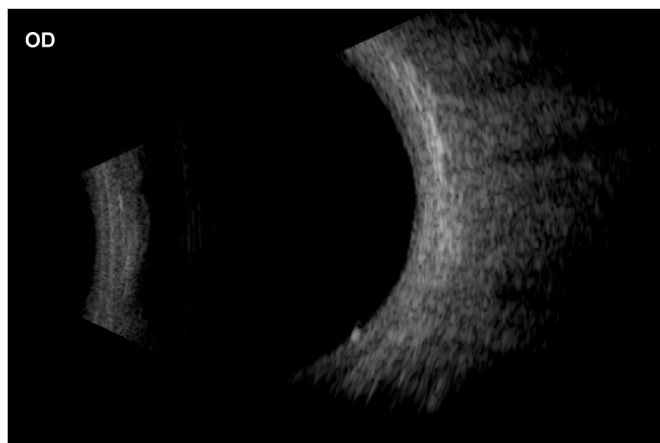
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**Fig. 2.** A, B: Montage of fundus photos of both eyes showing peripheral laser photocoagulation at 5 months of age. C, D: Fluorescein angiography of both eyes showing staining from peripheral laser photocoagulation in zone three.



**Fig. 3.** A, B: Montage of fundus photos of both eyes at 4 years of age. C, D: Fluorescein angiography of both eyes showing stable vascularized retinal folds with staining of peripheral fibrosis. E: Fundus photo showing an isolated astrocytic hamartoma in the right eye within an area of anterior retinal traction and vitreous condensation. F: Fluorescein angiography showing vascularized stalk with staining of the hamartoma in the right eye.



**Fig. 4.** B-scan ultrasonography of the right eye (OD) demonstrating a single calcified focus posterior to the equator.

LAC, CIN, CAM, AMB.

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