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# Multimodal imaging of white preretinal lesions in atypical familial exudative vitreoretinopathy: Case report and literature review

Liam D. Redden [a,*], Douglas S.M. Iaboni [b], Sarah van der Ende [c], Mathew Nightingale [d], Daniel Gaston [d], Christopher R. McMaster [c,e], Johane M. Robitaille [b,d,f], R. Rishi Gupta [b]

[a] Dalhousie Medical School, Dalhousie University, Halifax, NS, Canada
[b] Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada
[c] Department of Biochemistry & Molecular Biology, Dalhousie University, Halifax, NS, Canada
[d] Department of Pathology, Dalhousie University, Halifax, NS, Canada
[e] Department of Pharmacology, Dalhousie University, Halifax, NS, Canada
[f] Department of Pediatrics, Dalhousie University, Halifax, NS, Canada

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ABSTRACT

*Purpose:* To report a rare clinical finding of preretinal granules associated with atypical familial exudative vitreoretinopathy (FEVR) and perform a review of the literature.
*Observations:* An asymptomatic 18-year-old male was referred for unilateral peripheral avascular retina evaluation in association with presumed FEVR. He was first noted to have white preretinal granules on fundus examination at five years of age. The lesions remained unchanged over the subsequent years. Genetic testing did not reveal a pathogenic or likely pathogenic variant in a known FEVR gene. A review of the literature revealed five other cases of FEVR with similar findings.
*Conclusions and Importance:* Literature review suggests preretinal granules may present rarely in FEVR. Negative genetic screening of known FEVR genes in our patient with atypical FEVR suggests either a molecularly distinct etiology supporting the rarity of this association with FEVR or, alternatively, the presence of granules in developmental retinal vascular anomalies that are not specific to FEVR. Future study and genetic testing is necessary to better understand the cause of these preretinal granules and the clinical manifestations of FEVR.

## 1. Introduction

Familial exudative vitreoretinopathy (FEVR) is an, inherited, developmental vascular disorder of the retina first described by Criswick and Schepens in 1969.[1] FEVR is typically characterized by incomplete vascularization and hypoxia of the peripheral retina and may resemble retinopathy of prematurity. The disease presentation ranges from mild and asymptomatic, to severe with extensive vision loss due to retinal detachment, macular dragging, exudates and recurrent vitreous hemorrhages.[1]

FEVR is genetically heterogenous, with multiple inheritance patterns, and displays variable expressivity both within and between families.[2–5] Variants in FEVR genes listed in the Leiden open variation database (LOVD),[33] including *FZD4,*[6] *NDP,*[7] *LRP5,*[8] *TSPAN12,*[9] *ZNF408*[10] and *CTNNB1,*[11] account for less than 40% of cases, suggesting that more FEVR genes remain unidentified.[12] Other genes have been reported in association with FEVR with and without extraocular manifestations, but with the exception of *KIF11,*[13] most have been reported in rare cases with variable evidence to support a role in FEVR.[14–28]

In this report, we describe the multimodal imaging of an unusual patient with preretinal white lesions in the setting of FEVR and review the existing literature surrounding these lesions. We screened for variants in known FEVR genes and other genes that have been reported in association with a FEVR phenotype.

## 2. Case report

An asymptomatic 18-year-old male diagnosed with FEVR was referred for consideration of laser photocoagulation to the avascular retina in the left eye. Past birth, and family history were unremarkable. At 16 months of age, he suffered transient left sided weakness that fully recovered with no cause identified on extensive work-up including a CT

* Corresponding author. 2035West Victoria General Building, 1276 South Park Street, Halifax, NS, B3H 2Y9, Canada.
*E-mail address:* lm766098@dal.ca (L.D. Redden).

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scan and prothrombotic studies. At age 13, he had MRI, MRA, and MRV demonstrating a normal central nervous system and review of systems was negative.

On eye examination, visual acuity measured 6/6 in the right eye and 6/7.5 in the left eye. Intraocular pressure was 17 mmHg and 19 mmHg in the right and left eye, respectively. Anterior segment examination was unremarkable. Dilated examination of the right eye revealed a normal healthy appearing fundus with normal intravenous fluorescein angiography (IVFA) (Fig. 1A). In the left eye, there was temporal retinal dragging of the macula and arcades with supernumerary vessels. A zone of avascular retina was present extending from approximately 12 to 6 o'clock in the retinal periphery. Clusters of distinct white lesions were seen in the posterior pole superior to the optic nerve (Fig. 1B, arrowheads and Fig. 2). Fundus images from thirteen years prior showed the white lesions and peripheral avascular zone appeared stable. No hemorrhage or exudates were observed during the follow-up period.

On fundus autofluorescence (Fig. 1C and D) we were unable to appreciate the preretinal lesions. On IVFA (Fig. 1E and F), the material

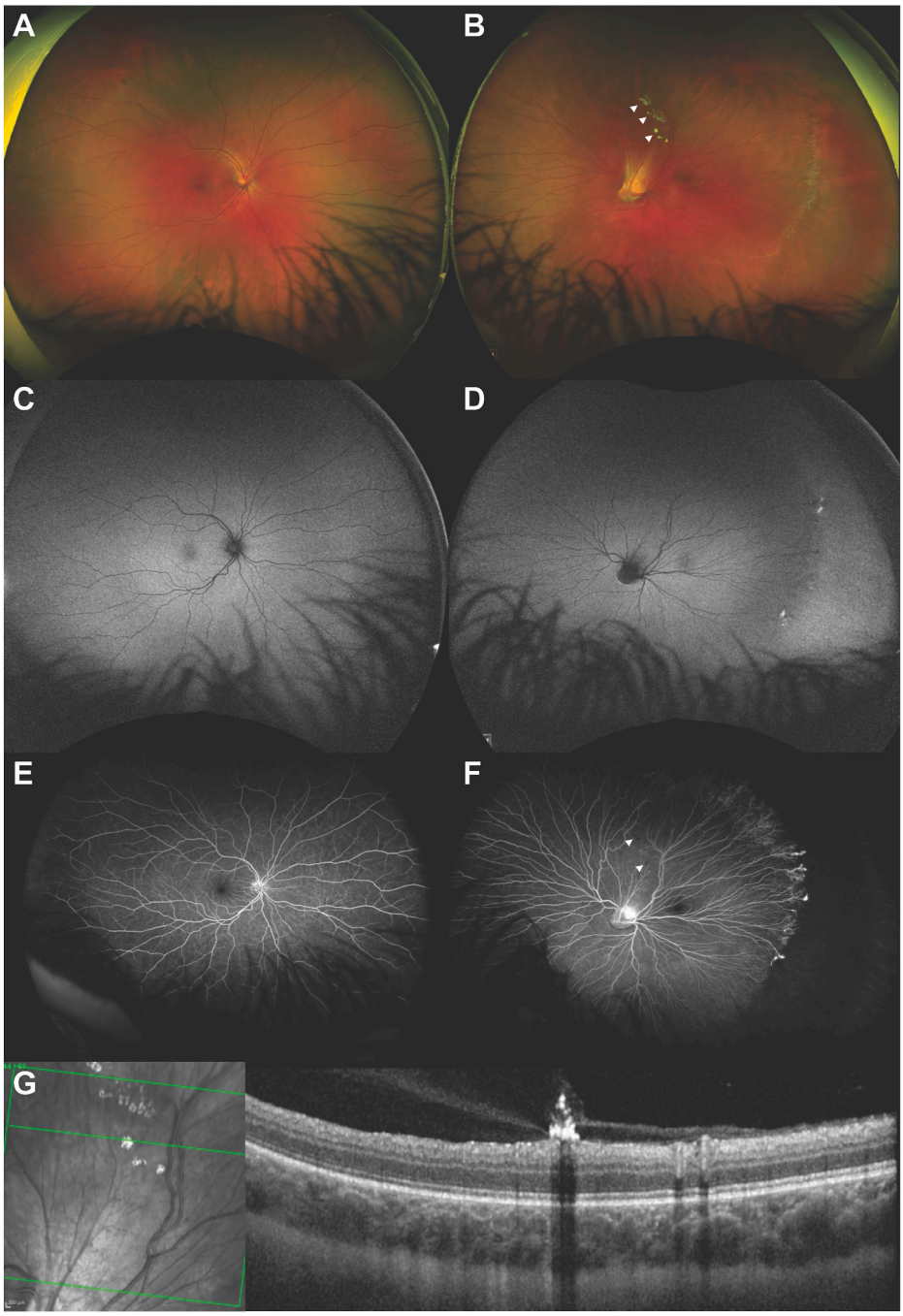


**Fig. 1. (A)** Optos pseudocolour ultra-widefield image of the right unaffected eye. **(B)** Optos pseudocolour ultra-widefield image of the left eye demonstrating temporal dragging of the arcades of macula and a peripheral avascular region. Arrowheads indicate the white preretinal lesions. **(C)** Optos fundus autofluorescence (FAF) of the right unaffected eye. **(D)** Optos FAF of the left eye demonstrating mild hyperautofluorescence of the peripheral avascular retina. The white preretinal lesions are not visible in the imaging modality. **(E)** Optos intravenous fluorescein angiography (IVFA) of the right unaffected eye. **(F)** Optos IVFA of the left eye demonstrating vessel leakage at the junction of the vascular and avascular peripheral retina. Arrowheads demonstrate areas of mild hypoautofluorescence aligned with the previously described white preretinal lesions. **(G)** Near infrared image on left, and corresponding optical coherence tomography image on right demonstrating hyperreflective preretinal granules.

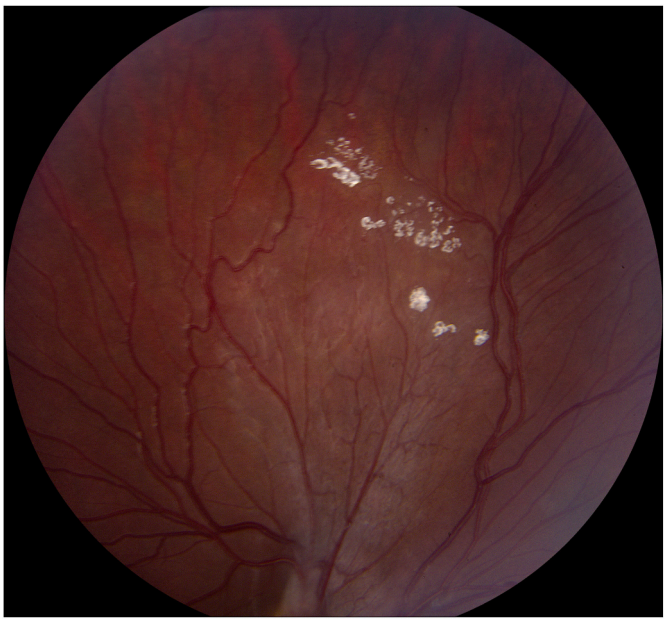

**Fig. 2.** True colour fundus image showing an enlarged view of the white preretinal granules. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

appeared marginally hypofluorescent in keeping with blockage (arrowheads). Leakage was visible along vessels at the intersection of the vascular and avascular retina in the left eye.

Macular optical coherence tomography (OCT) revealed a healthy appearing fovea in both eyes. OCT sections through the white lesions revealed preretinal hyperreflective material extending into the vitreous cavity with vitreous adhesions (Fig. 1G). The material cast shadows over the underlying retinal layers.

Both parents were examined and underwent IVFA. No significant retinal pathology in keeping with FEVR was identified. The patient and both parents were enrolled in a FEVR gene discovery study. The study was approved by the Research Ethics Board of the IWK Health Centre, Canada, and written consent was obtained in accordance with the Declaration of Helsinki. Whole exome sequence analysis performed in a research setting (i.e., not a clinical laboratory) using American College of Medical Genetics and Genomics (ACMG) guidelines did not reveal a pathogenic or likely pathogenic variant in the six known FEVR genes (*NDP, FZD4, LRP5, TSPAN12, ZNF408, CTNNB1*) and 18 genes associated with a phenotype overlapping FEVR (*KIF11, ATOH7, ILK, JAG1, CTNNA1, CTNND1, DLG1, TGFBR2, RCBTB1, COL9A1, DOCK6, ARHGAP31, NOTCH1, TUBGCP4, TUBGCP6, PLK4, CDK19, LAMA1*).

Ultimately, laser photocoagulation was not performed in this case as the patient was asymptomatic and had remained clinically stable despite degenerative changes in the areas of nonperfusion.

## 3. Literature review and discussion

We present a case manifesting white preretinal lesions in the presence of typical signs of FEVR on fundoscopy and IVFA. The incidence of FEVR was traditionally estimated at 1:10,000 in early gene discovery studies. However, a recent paper suggests a prevalence as high as 0.45 % in a multicentre review of 62,799 newborns without a history of prematurity who had eye examinations using wide-field digital imaging in the first month of life.[29] The associated finding of white preretinal lesions is rare. Three reports demonstrated similar lesions in five cases of FEVR. Details of these cases are provided in Table 1.

Day et al. were the first to report these lesions in FEVR through a photoessay in 2011. They hypothesized that the highly reflective pre- and intraretinal material was lipid in nature due to the well-circumscribed appearance on OCT and golden colour on fundus photography. As a result, Day et al. termed the lesions preretinal and intraretinal exudates.[30]

In 2013, Shimouchi et al. reported two cases of FEVR with vitreomacular interface findings, one of which had similar preretinal lesions. Both cases had peri-foveal posterior vitreous detachments, which the authors believed were accelerated by peripheral neovascularization. The report postulated the white material may be the result of precipitate formation in the vitreous cavity induced by neovascular vitreous traction.[31]

Johnson et al. presented a retrospective case series from Emory Eye Center (GA, USA) of three patients with similar white preretinal granules in the context of FEVR. One patient required vitrectomy with membrane dissection, during which, the granules were removed and submitted for analysis. Histopathologic study revealed a crystalline material with macrophages and fibrocytes.[32]

Among the five reported cases, ages ranged from 6 months to 18 years.[30–32] Our patient was 5 years old at the time of discovery of the lesions. It is not known how long the preretinal lesions may have been present for in our case and follow-up of 13 years in our case and up to 6 years in the reports shows the lesions appear to be indolent and remain stable over time.[33] The locations of the lesions do not appear to be predictable and range in the reports from being outside the superior/-inferior arcade to being parafoveal.[30,32] Of note however, there are no reports of the lesions being present in the avascular zone of the peripheral retina.

None of the previous reports mention genetic testing results or presence of extraocular manifestations. Further study grouping pedigrees with this rare feature could identify a novel FEVR gene should this represent a distinct form of FEVR, as we did not identify a pathogenic or likely pathogenic variant using an extensive FEVR gene panel that included genes from reports of rare associations.

## 4. Conclusions

The rarity of these preretinal granules makes it difficult to elucidate a cause. Prior articles propose its appearance may be linked to areas of vitreoretinal adhesion or tend to be located at the junction of vascular and avascular retina. The ethnicity, age at diagnosis, location, and disease severity vary considerably among the reported cases. Additionally, our article is the first to provide genetic testing, so it is unclear if there could be a genetic component. Overall, although these lesions are rare and have limited long-term follow up, they appear to be indolent and non-progressive. Genetic testing in future cases could help us elaborate the cause behind these findings and may help us to expand and better understand the clinical manifestations of FEVR.

## 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

**Liam D. Redden:** Data curation, Investigation, Methodology,

**Table 1**
Summary of the published similar cases of white preretinal lesions in the setting of FEVR.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Publication | Johnson et al., 2017 | Johnson et al., 2017 | Johnson et al., 2017 | Day et al., 2011 | Shimouchi et al., 2013 |
| Age | 6 years | 12 years | 10 months | 6 months | 14 years |
| Sex | Female | Male | Male | Not documented | Male |
| Race/Ethnicity | Asian | Hispanic | African American | Not documented | Not documented |
| Laterality | Unilateral (OD) | Unilateral (OD) | Bilateral | Bilateral | Unilateral (OD) |
| Symptoms | Not documented | Decreased vision | Not documented | Not documented | Not documented |
| Initial VA | 20/100 | Counting fingers | Not documented | Not documented | 20/30 |
| Anterior Segment | Normal | Normal | Not documented | Not documented | Not documented |
| Fundus Examination | Peripheral zone of avascular retina for 360°, mild subretinal yellow exudate, and preretinal fibrosis superotemporally. A cluster of white preretinal granules just outside the superotemporal arcade. | Anomalous and tilted disk with temporal retinal dragging. Distinctive white granules clustered outside the inferior arcade vessels. A zone of avascular retina in the temporal periphery. | Peripheral zones of avascular retina in both the eyes. No retinal dragging, exudation, or neovascularization. Conspicuous white lesions were found temporal to the macula in both eyes. | Retinal exudates in the macula of the right eye, and in the fovea and along the superotemporal and inferotemporal arcades of the left eye | White material on the parafovea of the right eye |
| OCT | Not documented | Not documented | Not documented | (Hand held SD-OCT) Highly reflective preretinal material in the right eye, and both preretinal and intraretinal material in the left eye corresponding to the areas of exudates seen in each eye. | (SD-OCT) Perifoveal PVD in the right eye and numerous small deposits, which appeared as rodshaped attachments perpendicular to the parafoveal face without intraretinal and subretinal materials beneath the posterior hyaloid face that corresponded to the white material on the fundus examination |
| Red-free imaging | Not documented | Highlighted white granule clusters | Not documented | Not documented | Not documented |
| Fluorescein angiography | Not documented | White granule clusters not apparent | Not documented | Not documented | Circumferential peripheral avascular area and peripheral neovascularization temporally |
| Histopathology | Crystalline material surrounded by fibrocellular tissue composed of fibrocytes | Not documented | Not documented | Not documented | Not documented |
| Transmission electron microscopy | Macrophages containing intracytoplasmic inclusions of varying electron density, as well as spindle shaped cells (fibrocytes) containing fusiform nuclei and dilated cisternae of rough endoplasmic reticulum. Also crystal-like structures containing a regular pattern evident on higher magnification | Not documented | Not documented | Not documented | Not documented |
| Energy dispersive x-ray analysis | Elemental constituents mainly carbon and oxygen with a smaller (less than 3 % by weight) amount of fluorine | Not documented | Not documented | Not documented | Not documented |
| Treatment | Laser photocoagulation of peripheral avascular retina, vitrectomy and membrane dissection | Laser photocoagulation of peripheral avascular retina | Laser photocoagulation of peripheral avascular retina | Not documented | Not documented |
| Final VA | Not documented | Not documented | Not documented | Not documented | Not documented |
| Follow up time | 6 years | 6 years | 5 years | Not documented | Not documented |

Writing – original draft, Writing – review & editing. **Douglas S.M. Iaboni:** Supervision, Writing – original draft, Writing – review & editing. **Sarah van der Ende:** Writing – original draft, Software, Investigation, Data curation. **Mathew Nightingale:** Investigation, Data curation. **Daniel Gaston:** Data curation, Investigation. **Christopher R. McMaster:** Data curation, Investigation. **Johane M. Robitaille:** Supervision, Writing – review & editing. **R. Rishi Gupta:** Conceptualization, Supervision, Writing – review & editing.

## 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.

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