Case Report

Ophthalmology and Allied Sciences
Volume 12 Number 1/January-June 2026
**DOI:** 10.21088/oas.2454.7816.12126.4

# Familial Foveal Hypoplasia and Review of Literature

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**How to cite this article:**

***Vijay Kumar Maurya, Jagriti Rana, Arti Singh et. al,*** Familial Foveal Hypoplasia and Review of Literature. Ophthalmol Allied Sci. 2026;12(1): 27–32.

## ABSTRACT

***Objective:*** To describe a familial presentation of isolated foveal hypoplasia (FH) with detailed clinico-imaging correlation based on fundus photography and spectral-domain optical coherence tomography (SD-OCT), highlighting the diagnostic value of multimodal imaging in this rare condition.

***Methods:*** A 22-year-old male proband and his younger sister underwent complete ophthalmic evaluation including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, dilated fundus examination, Topcon Maestro2 SD-OCT with radial macular scanning protocol, and whole-exome molecular genetic testing.

***Results:*** BCVA was 20/200 bilaterally in the proband. Fundus photography revealed absence of the foveal reflex in both eyes, with an incidental chorioretinal lesion in the left eye. SD-OCT demonstrated absent foveal pit with diffuse macular thickening (OD mean 259.9 µm; OS mean 279.6 µm) and persistence of inner retinal layers over the foveal center bilaterally, consistent with Grade 3 FH. A pathogenic FRMD7 gene variant was identified on whole-exome sequencing. His sibling harbored the same variant in heterozygous form.

***Conclusions:*** Multimodal imaging – combining fundus photography with SD-OCT macular thickness mapping – provides objective, quantifiable documentation of foveal maldevelopment and enables grading that guides prognosis and counseling in familial FH.

## KEYWORDS:

• Foveal Hypoplasia • Frmd7 Gene • SD-OCT • Macular Thickness • Fundus Photography • Familial • X-Linked Nystagmus

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➢ **Received:** 20.07.2026 ➢ **Accepted:** 22.08.2026

*Abbreviations*

FH – foveal hypoplasia; SD-OCT – spectral-domain optical coherence tomography; BCVA – best-corrected visual acuity; ETDRS – Early Treatment Diabetic Retinopathy Study; FRMD7 – FERM domain-containing protein 7; OD – oculus dexter (right eye); OS – oculus sinister (left eye); OU – oculus uterque (both eyes)

## INTRODUCTION

Foveal hypoplasia (FH) is a developmental anomaly characterized by failure of normal foveal pit formation during embryogenesis, resulting in persistence of inner retinal layers over the foveal center and consequent loss of high-resolution central vision.[1] The fovea normally undergoes pit formation and photoreceptor specialization by approximately 15 weeks of gestation; disruption of this process produces the structural hallmarks of FH that are now well-characterized on spectral-domain optical coherence tomography (SD-OCT).[2,3]

FH is most commonly encountered in association with albinism, aniridia, and other systemic syndromes, but isolated familial presentations are considerably rarer.[4] Mutations in FRMD7, SLC38A8, PAX6, and NR2E3 have been implicated in the pathogenesis of isolated FH, with FRMD7 being the most frequently identified cause of X-linked idiopathic infantile nystagmus and co-occurring FH.[5,6]

Multimodal imaging – particularly fundus photography combined with SD-OCT macular thickness mapping – has become the cornerstone of objective diagnosis and structural grading of FH.[7,9] Quantitative macular thickness data from ETDRS maps provide reproducible metrics for disease documentation and facilitate longitudinal monitoring. We report a familial case of isolated FH in two siblings due to an FRMD7 mutation, with clinico-imaging correlation based on fundus photography and Topcon Maestro2 SD-OCT findings.

## CASE PRESENTATION

A 22-year-old male (Patient ID: anonymized; scan date: 01/03/2025) was referred to the retina clinic with a complaint of reduced central vision in both eyes since early childhood. His parents had noted difficulty with reading and facial recognition from a young age. He had no systemic illness and no features of albinism, aniridia, or other syndromic associations.

BCVA was 20/200 in both eyes with a stable manifest refraction. Anterior segment slit-lamp examination was unremarkable; intraocular pressure was within normal limits bilaterally.

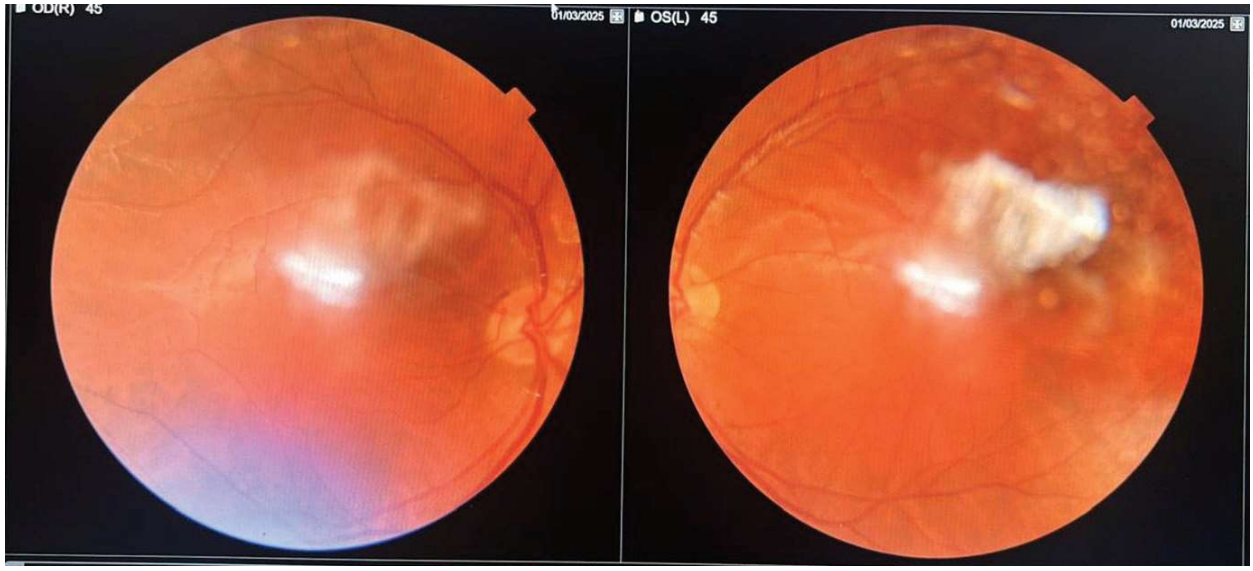


**Figure 1:** Wide-field fundus photographs (45°, OD right; OS left)
OD: absent foveal reflex, flat featureless macula, normal optic disc and vasculature. OS: absent foveal reflex.

**Fundus Examination (Figure 1)**

Wide-field fundus photography (45°, IMAGEnet system) of the right eye (OD) demonstrated a flat, featureless macula with complete absence of the foveal reflex and no foveal pit highlight. The optic disc was healthy with a normal cup-to-disc ratio; retinal vasculature was of normal caliber and course. No pigmentary disturbance, subretinal fluid, or peripheral pathology was identified in OD.

The left eye (OS) similarly exhibited absent foveal reflex and a flat macula. Additionally, a well-demarcated, bright white, hyperreflective lesion was identified in the superotemporal macular quadrant of OS, with associated underlying pigmentary change, consistent with a chorioretinal scar. This lesion did not obscure the central foveal area but was documented as an incidental finding warranting longitudinal monitoring. No active neovascular membrane or subretinal hemorrhage was noted. The optic disc and peripheral retina in OS were otherwise unremarkable.

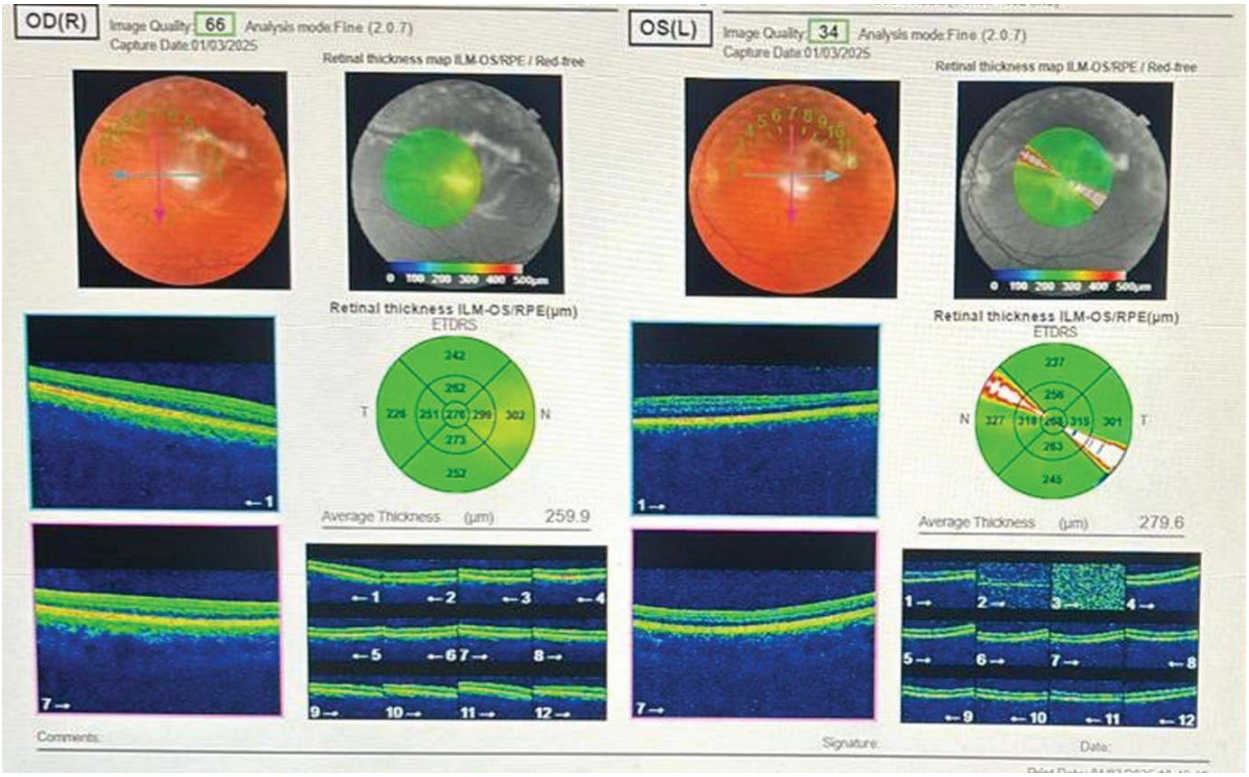


**Figure 2:** Topcon Maestro2 SD-OCT Radial Report (OU, 01/03/2025). OD (left panel, IQ 66): mean macular thickness 259.9 µm; ETDRS map and B-scans show absent foveal pit with diffuse macular thickening and inner retinal layer persistence. OS (right panel, IQ 34): mean macular thickness 279.6 µm; ; ETDRS map and B-scans show absent foveal pit with diffuse macular thickening and inner retinal layer persistence

**Spectral-Domain OCT – Radial Macular Protocol (Figure 2)**

SD-OCT was performed using a Topcon Maestro2 device with a radial 6.0 mm scan protocol (1024 × 12 lines, Fine analysis mode 2.0.7). ETDRS retinal thickness maps (ILM–OS/RPE, red-free) were generated for both eyes.

**Right eye (OD):** Image quality score was 66 (adequate). The ETDRS map demonstrated diffuse macular thickening with a mean macular thickness of 259.9 µm. The central subfield thickness measured approximately 279–302 µm across radial scans. B-scan cross-sectional images showed a shallow, poorly defined foveal contour with complete absence of the foveal pit depression. Persistence of inner retinal layers – including the ganglion cell layer and inner plexiform layer – over the presumed foveal center was evident, consistent with Grade 3 foveal hypoplasia. The outer nuclear layer showed relative preservation without photoreceptor disruption.

**Left eye (OS):** Image quality score was 34 (suboptimal,). Mean macular thickness was 279.6 μm, with central subfield values of 315–319 μm – greater than OD. B-scan images confirmed absent foveal pit with macular thickening. Inner retinal layer persistence over the foveal center was present in OS as in OD.

These bilateral SD-OCT findings – absent foveal pit, inner retinal layer persistence, and diffuse macular thickening without photoreceptor specialization – confirm Grade 3 foveal hypoplasia according to the Thomas et al. structural grading system.[9]

### Genetic Testing and Family Screening

Following disclosure of similar visual symptoms in the proband's younger sister (18 years, female), she underwent identical ophthalmic and OCT evaluation. BCVA was 20/160 bilaterally, with SD-OCT confirming absent foveal pit and macular thickening comparable to her brother's findings. Both parents were visually asymptomatic and had normal foveal architecture on OCT.

Whole-exome sequencing (performed after informed consent) identified a hemizygous pathogenic variant in the FRMD7 gene (OMIM 300628) in the proband, with the same variant present in heterozygous form in his affected sister and in their carrier mother. This pattern is consistent with X-linked inheritance. Both parents were counseled regarding recurrence risk and the implications for future offspring.

Both affected siblings were prescribed low-vision magnification aids and referred for visual rehabilitation and orientation and mobility training. Written informed consent for publication was obtained.

## DISCUSSION

This case illustrates the diagnostic value of integrating fundus photography with SD-OCT macular mapping in the workup of familial FH. The bilateral absence of the foveal reflex on fundus photography – a subtle sign that can be overlooked on routine dilated examination – was objectively corroborated by SD-OCT demonstrating absent foveal pit and diffuse macular thickening bilaterally.[1,7]

### Clinico-Imaging Correlation

The ETDRS macular thickness values in this case – OD mean 259.9 μm and OS mean 279.6 μm – are significantly above the normative central subfield thickness (typically 230–250 μm in healthy adults), reflecting the persistent inner retinal lamination that characterizes FH.[3,9]

The suboptimal image quality score for OS (IQ 34 vs. OD IQ 66) is clinically important: reduced scan quality can affect segmentation accuracy and therefore macular thickness reliability. The editorial note to reviewers is that the OS values should be interpreted with this caveat; the structural diagnosis of FH in OS, however, remains unambiguous given the unequivocal B-scan appearances.

### Genetic Basis and Inheritance

FRMD7 encodes a FERM domain-containing protein expressed during retinal neurogenesis. Pathogenic FRMD7 variants are the most commonly identified genetic cause of X-linked idiopathic infantile nystagmus (XLIIN), and SD-OCT studies have consistently demonstrated FH as a co-occurring structural correlate in affected individuals.[5,10] Betts-Henderson et al. showed that FRMD7 regulates neuronal outgrowth, providing a mechanistic basis for foveal maldevelopment.[10]

The hemizygous state in the proband (male), heterozygous expression in his affected sister, and carrier status in the asymptomatic mother follow the expected X-linked pattern. Phenotypic expression in heterozygous females is variable; skewed X-inactivation may account for clinical involvement in the proband's sister.[6]

### Diagnostic and Management Considerations

The Thomas *et al.* four-grade OCT classification is a widely adopted tool for standardized reporting of FH severity: Grade 1 (absent foveal avascular zone only) through Grade 4 (hypoplasia of all retinal layers).[9] The present case satisfies Grade 3 criteria – absent foveal pit with absent photoreceptor layer specialization – based on both the B-scan appearances and the quantitative thickness data.

There is currently no disease-modifying treatment for FH. Management is centered

on low-vision rehabilitation and genetic counseling.[4] In cases where nystagmus co-exists (as with FRMD7 mutations), contact lens correction may reduce nystagmus amplitude and improve acuity in some patients by dampening the afferent visual signal.[11] Optical coherence tomography angiography (OCTA) would be a useful adjunct to assess the foveal avascular zone in future evaluations.

## CONCLUSION

Familial foveal hypoplasia due to FRMD7 mutation presents with characteristic multimodal imaging findings: absent foveal reflex on fundus photography and absent foveal pit with diffuse macular thickening and inner retinal layer persistence on SD-OCT. Quantitative ETDRS macular thickness mapping provides objective documentation of disease grade and inter-eye asymmetry. The incidental chorioretinal scar in OS in this case highlights the importance of thorough retinal examination beyond the fovea in all patients with unexplained central visual impairment. Early genetic evaluation enables appropriate counseling of affected families and screening of at-risk relatives.

**Acknowledgements:** None.

**Sources of Funding:** None.

**Disclosures:** None.

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