# Commentary: Familial exudative vitreoretinopathy-The masquerade in pediatric retinal disorders

This issue of IJO features an interventional study discussing the clinical profile, management, and outcomes of pediatric macula-off rhegmatogenous retinal detachment (RRD) secondary to familial exudative vitreoretinopathy (FEVR).[1] FEVR is a rare inherited disorder of retinal angiogenesis, characterized by phenotypic and genotypic heterogenicity.[2] Phenotypic expression may range from the presence of temporal avascular peripheral retina in an asymptomatic patient to extensive subretinal exudation, florid fibrovascular proliferation, retinal folds, tractional retinal detachment (RD) or RRD, or severe retinal dysplasia at birth resulting in severe visual dysfunction and even total blindness.[2] Treatment options include observation, laser photocoagulation or cryotherapy, anti-vascular endothelial growth factor (anti-VEGF) injection and scleral buckle, and/or pars plana vitrectomy (PPV), depending upon the stage of disease at presentation.[2]

Management of RRD in FEVR is complicated by its presentation in younger age as well as by the underlying abnormal vitreoretinal interface, which is more adherent and difficult to completely separate from the retina, resulting in postoperative pre-retinal proliferation and recurrent RD.[3] Unique surgical problems are associated with these RRDs, especially in the presence of associated falciform retinal folds.[3] Where peripheral breaks with falciform folds can be supported on a scleral buckle, posterior retinal breaks in eyes with falciform folds necessitating PPV and large posterior relaxing retinectomies result in particularly dismal outcomes.[3]

Due to phenotypic variability, improper and delayed diagnosis is the biggest hurdle in the management of FEVR. When presenting in the neonatal period, it can masquerade other pediatric retinal disorders like retinopathy of prematurity (ROP) and persistent fetal vasculature (PFV).[2] A small subset of premature infants who exhibit retinal findings more characteristic of FEVR than ROP have been described as ROPER (ROP vs. FEVR) by Gologorsky *et al*.[4] These eyes behave more like FEVR, with a less predictable and more progressive course of disease in long term.[4] FEVR can mimic PFV, especially if associated with "knifelike retinal folds "extending from the optic disk radially to the peripheral retina and anteriorly to the ciliary processes.[2] It is quite possible for a patient to have advanced FEVR findings in one eye and grossly normal other eye, further creating confusion with PFV. The stalk in PFV, unlike the falciform fold in FEVR, is not typically a retinal fold, but a hyaloid stalk of persistent vascular tissue that extends from the optic nerve to the posterior lens surface.[5]

Accurate diagnosis of FEVR is best done by careful clinical examination coupled with fundus fluorescein angiography (FFA) and genetic testing wherever possible. FFA enhances the diagnostic sensitivity because subtle vascular changes in the periphery or even in the posterior pole can easily be overlooked by a routine fundus examination.[2] Wide-field retinal imaging is particularly helpful to detect asymptomatic family members.

Because of phenotypic variations, genetic testing may become essential in some cases to establish the diagnosis. The inheritance pattern of FEVR may be autosomal dominant (AD; most common), autosomal recessive (AR), or X-linked recessive (XL-R), and the common genes implicated so far include *NDP*, *FZD4*, *LRP5*, *TSPAN12*, *ZNF408* and *KIIF11*.[2,6,7] The first four genes result in mutations in the "Norrin/β-catenin signaling pathway," which plays a pivotal role in vascular morphogenesis in the eye.[2] *KIF11*, localized to the spindle microtubules, is involved in the mitotic progression and growth of the retinal vessels.[6] The *ZNF408* protein has been implicated in abnormal retinal vascularization and trunk vascularization in zebrafish.[7] While almost all patients with *NDP* mutations

are reported to have a severe presentation, milder phenotypes ranging from stage 2 to stage 5 have been seen in eyes with *LRP5* mutations.[8] Disease phenotype is reportedly more bilaterally symmetrical in patients with *KIFF11*, *TSPAN12*, and *NDP* gene mutations compared to patients with *LRP5* and *FZD4* mutations.[9] Widespread chorioretinal degeneration may additionally be present in cases with *KIFF11* and *NDP* mutations, along with neurodevelopmental delay and microcephaly.[10] Genetic testing in FEVR is important for diagnosis, better understanding of the disease, and prognostication. Knowledge of the gene mutation can also facilitate the molecular prenatal analysis of fetal DNA; this along with antenatal ultrasound can be used to predict FEVR in at-risk babies.[11] Timely intervention in the early neonatal period itself can prevent total blindness in some at-risk babies.

FEVR, a clinically and genetically heterogeneous disorder, requires a high index of suspicion, careful examination, timely management, and long-term follow-up. Increased genetic testing in these patients will further improve our understanding of the disease. Awareness and education of parents as well is of paramount importance to reduce the risk of bilateral total blindness due to FEVR.

***Parveen Sen, Janani Sreenivasan***

Department of Vitreo-Retina, Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, Chennai, Tamil Nadu, India

Correspondence to: Dr. Parveen Sen, Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18 College Road, Chennai, Tamil Nadu - 600 006, India.
E-mail: parveensen@gmail.com

## References

1. Agrawal V, Kalia S. Management and surgical outcomes of pediatric retinal detachment associated with familial exudative vitreoretinopathy – Our experience at a tertiary care ophthalmic center in North India. Indian J Ophthalmol 2022;70:2490-6.
2. Sızmaz S, Yonekawa Y, T Trese M. Familial exudative vitreoretinopathy. Turk J Ophthalmol 2015;45:164-8.
3. Sen P, Singh N, Rishi E, Bhende P, Rao C, Rishi P, *et al*. Outcomes of surgery in eyes with familial exudative vitreoretinopathyassociated retinal detachment. Can J Ophthalmol 2020;55:253-62.
4. Gologorsky D, Chang JS, Hess DJ, Berrocal AM. Familial exudative vitreoretinopathy in a premature child. Ophthalmic Surg Lasers Imaging Retina 2013;44:603-5.
5. Tian T, Chen C, Zhang X, Zhang Q, Zhao P. Clinical and genetic features of familial exudative vitreoretinopathy with only-unilateral abnormalities in a Chinese cohort. JAMA Ophthalmol 2019;137:1054-8.
6. Wang Y, Smallwood PM, Williams J, Nathans J. A mouse model for kinesin family member 11 (Kif11)-associated familial exudative vitreoretinopathy. Hum Mol Genet 2020;29:1121-31.
7. Collin RW, Nikopoulos K, Dona M, Gilissen C, Hoischen A, Boonstra FN, *et al*. ZNF408 is mutated in familial exudative vitreoretinopathy and is crucial for the development of zebrafish retinal vasculature. Proc Natl Acad Sci U S A 2013;110:9856-61.
8. Rao FQ, Cai XB, Cheng FF, Cheng W, Fang XL, Li N, *et al*. Mutations in LRP5, FZD4, TSPAN12, NDP, ZNF408, or KIF11 genes account for 38.7% of Chinese patients with familial exudative vitreoretinopathy. Invest Ophthalmol Vis Sci 2017;58:2623-9.
9. Tao T, Xu N, Li J, Li H, Qu J, Yin H, *et al*. Ocular features and mutation spectrum of patients with familial exudative vitreoretinopathy. Invest Ophthalmol Vis Sci 2021;62:4.
10. Yang J, Xiao X, Li S, Mai G, Jia X, Wang P, *et al*. Severe exudative vitreoretinopathy as a common feature for CTNNB1, KIF11 and NDP variants plus sector degeneration for KIF11. Am J Ophthalmol 2021;235:178-87.
11. Liu J, Zhu J, Yang J, Zhang X, Zhang Q, Zhao P. Prenatal diagnosis of familial exudative vitreoretinopathy and Norrie disease. Mol Genet Genomic Med 2019;7:e00503.



**Access this article online**

**Quick Response Code:**

**Website:** www.ijo.in

**DOI:** 10.4103/ijo.IJO_216_22

**Cite this article as:** Sen P, Sreenivasan J. Commentary: Familial exudative vitreoretinopathy-The masquerade in pediatric retinal disorders. Indian J Ophthalmol 2022;70:2496-7.