Underlying Disease in Atypical Retinopathy of Prematurity

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• BACKGROUND AND OBJECTIVE: **Retinopathy of prematurity (ROP), familial exudative vitreoretinopathy (FEVR), and telomere biology disorders (TBD) are classified as distinct diseases. However, emerging genetic research and evidence on multimodal imaging suggest a spectrum along which ROP may overlap with FEVR or TBD.**

• DESIGN: **Retrospective case series.**

• METHODS: **This was an institutional review board-approved, retrospective study. A literature review was performed, and medical records of all patients with phenotypic ROP evaluated by the pediatric retina service at Bascom Palmer Eye Institute from March 1, 2019 to July 30, 2023 were analyzed.**

• RESULTS: **Eighteen patients with phenotypic and genetically confirmed FEVR or TBD were identified. Of these, the initial diagnosis was ROP with preterm gestational age ($n = 11$, 57.9%) or ROP at moderate to late preterm gestational age ($n = 8$, 42.1%). Final diagnosis for 15 patients (78.9%) was FEVR, and final diagnosis for 4 patients (21.1%) was TBD. The most common genetic variants in the FEVR group were identified in the genes *LRP5* ($n = 5$, 33.3%) and *FZD4* ($n = 3$, 20%), and in the TBD group, *CTC1* ($n = 3$; 75%). The mean age at diagnosis was 5.7 years old (range 0.3-36.7 years).**

• CONCLUSIONS: **The authors reinforce the classification of ROPER (ROP and FEVR) and introduce the term, ROPMERE (ROP and TBD), to classify these patients in a way that reflects their clinical presentation and underlying genetic diagnosis. Identification of this subset of patients will allow for sustained surveillance of infants with these diseases. (Am J Ophthalmol 2025;274: 67–75.**

INTRODUCTION

Retinopathy of prematurity (ROP) and familial exudative vitreoretinopathy (FEVR) share many clinical characteristics but are classified as separate entities. Underlying both diseases is an abnormal development of retinal vasculature, and therefore, both have secondary retinal complications, including peripheral avascularity, neovascularization, vitreous hemorrhage, subretinal exudation, vascular dragging, retinal folds and detachments.[1-3] Reports have documented patients with clinical features of advanced ROP who possess genetic variants associated with FEVR. John et al.[4] specifically introduced the term ROPER (ROP vs FEVR) to better describe these premature infants who exhibit clinical characteristics of ROP and possess disease-causing genetic pathogenic variant associated with FEVR.

Telomere biology disorders (TBDs) are a group of disorders caused by genetic abnormalities that result in prematurely short telomeres. Pathologically shortened telomeres increase susceptibility to inaccurate DNA replication and trigger cellular senescence or apoptosis that result in different phenotypes with variable penetrance.[5,6] TBDs have a strong association with prenatal and perinatal complications, including intrauterine growth restriction (IUGR).[7] Retinal findings include bilateral exudative retinal telangiectasias, avascularity, exudation, and neovascularization. Because of variable clinical presentation and rarity of cases, TBDs are often unrecognized and underdiagnosed.[8]

Although ROP, FEVR, and TBDs possess different pathophysiology, they share various clinical similarities. In our clinical experience on the pediatric retina service at Bascom Palmer, we have encountered infants who were premature at birth and exhibited characteristics of atypical ROP. Our study on premature infants reinforces the term ROPER for infants that exhibit clinical features of advanced or atypical ROP but possess disease-causing genetic variant confirming a diagnosis of FEVR. Furthermore, our study proposes the introduction of ROPMERE, a new classification for infants that exhibit clinical features of advanced or atypical ROP but possess disease-causing genetic variant confirming an underlying diagnosis of TBD.

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METHODS

This study was a retrospective analysis of patients with a clinical appearance of ROP but underlying diagnosis of FEVR or TBD, who underwent genetic evaluation and multimodal imaging during examination under anesthesia at Bascom Palmer Eye Institute from March 1, 2019, to July 30, 2023. This study was approved by the University of Miami institutional review board and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from the patient or the patients' parents. Inclusion criteria included a clinical diagnosis of atypical ROP from a preexisting log of patients seen by a single provider (A.M.B.). Diagnosis was determined by a pediatric retina specialist (A.M.B.) based on clinical diagnostic criteria and genetic testing results. Next-generation sequencing technology (Invitae; Labcorp Genetics, United States) was used to perform gene sequencing in the cases. Genetic testing was considered positive if the results demonstrated a pathogenic variant in a gene that has previously been linked to the development of FEVR or TBD. Data collected from medical records included demographic information, medical history, ophthalmic examination, genetic testing, and prior treatments. Referral diagnosis of ROP was determined by conducting a chart review and reviewing history obtained from the patient during clinical encounters.

RESULTS

Thirty-eight eyes from 19 patients met the inclusion criteria. All patients with clinical features of ROP possessed positive genetic results indicating an underlying diagnosis of FEVR or TBD. Fifteen patients were male (15/19, 78.9%), and 4 were female (4/18, 21.1%). Mean age at first visit was 4.1 years old (range 0.1-23.8 years). Mean age at time of diagnosis of FEVR or TBD was 5.7 years old (range 0.3-36.7 years).

Fifteen patients (15/19, 78.9%) were diagnosed with FEVR, and 4 (4/19, 21.1%) were diagnosed with TBD. The most common genes implicated among the patients with FEVR included *LRP5* (5/15, 33.3%), *FZD4* (3/15, 20%), *TSPAN12* (2/15, 13.3%), *CTNNA1* (2/15, 13.3%), *KIF11* (1/15, 6.7%), *NDP* (1/15, 6.7%), and *ZNF408* (1/15, 6.7%). The most common genes implicated among the patients with TBD included *CTC1* (3/4, 75%) and *ACD* (1/4, 25%). Among the patients referred for FEVR, family history was non-contributory. Among the TBD patients, there were 2 patients with *CTC1* variant who were brothers (Figure 1-5).

Eleven patients (11/19, 57.9%) had an initial diagnosis of ROP with preterm gestational age (<32 weeks), and 8 patients (8/19, 42.1%) were given a diagnosis of ROP at moderate to late preterm gestational age (≥32 weeks). The mean gestational age at birth was 29.4 weeks (Table 1).

At the time of presentation, incomplete peripheral vascularization was seen in 34 eyes (34/38, 89.5%), tortuous vessels in 14 eyes (14/38, 36.8%), neovascularization in 10 eyes (10/38, 26.3%), retinal detachment (RD) in 9 eyes (9/38, 23.7%), exudation in 6 eyes (6/38, 15.8%), retinal dragging in 4 eyes (4/38, 10.5%), vitreous hemorrhage in 3 eyes (3/38, 7.9%), fovea plana in 3 eyes (3/38, 7.9%), telangiectatic vessels in 3 eyes (3/38, 7.9%), terminal arborization of vascular branches (2/38, 5.3%), aneurysmal dilation of arterioles (2/38, 5.3%), straightening of vessels in 1 eye (1/38, 2.6%), scattered hemorrhages in 1 eye (1/38, 2.6%), patches of hyperpigmentary change in 1 eye (1/38, 2.6%), and coloboma in 1 eye (1/38, 2.6%) (Table 2). Visual acuity (VA) at presentation was 20/200 or better in 10 eyes (10/20 eyes, 50%), worse than 20/200 in 8 eyes (10/20 eyes, 50%), and not measurable in the remaining 18 eyes.

Regarding treatment, 24 eyes (24/38, 63.2%) underwent intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA) injection, 25 eyes (25/38, 65.8%) received laser photocoagulation, 19 eyes (19/38, 50%) underwent injection of sub-tenon's Kenalog, and 2 eyes (2/38, 5.3%) underwent surgical repair with combined pars plana lensectomy and vitrectomy. All patients treated with laser photocoagulation or bevacizumab required multiple sessions or injections at the time of study completion. Final best corrected VA was better than or equal to 20/200 in 15 eyes (15/26, 57.7%), worse than 20/200 in 11 eyes (11/26, 42.3%), and not measurable in the remaining eyes. Mean follow-up time at our institution was 36.5 months (range 0-164 months).

DISCUSSION

In this study, we present a group of premature infants displaying clinical characteristics of advanced or atypical ROP and later identified to have an underlying diagnosis of FEVR or TBD after undergoing genetic testing. This highlights the challenge of diagnosing FEVR and TBD in preterm infants and the importance of genetic testing.

ROP and FEVR are currently classified as distinct diseases. However, emerging genetic research and evidence on fluorescein angiography (FA) suggest overlap in clinical features, making differentiation challenging. FEVR in a premature infant can be distinguished from ROP or atypical ROP in that exudates are often present on examination. FA findings of patients with ROPER include irregular 'sprouts' of vascularization at the vascular/avascular junction, distinct pruning of vessels, pinpoint areas of hyperfluorescence, and segmental areas of vascular leakage.[4,9] Furthermore, ROP and FEVR are often distinguished from each other by evaluating the stability or regression of the disease over time. ROP, as a disease, tends to regress as the

TABLE 1. Demographics and Genetic Variants in Patients With Atypical ROP.

Total patients with atypical ROP	19
Patients with genetically confirmed FEVR variants	15 (78.9%)
LRP5	5 (33.3%)
FZD4	3 (20%)
CTNNA1	2 (13.3%)
TSPAN12	2 (13.3%)
KIF11	1 (6.7%)
NDP	1 (6.7%)
ZNF408	1 (6.7%)
Patients with genetically confirmed TBD variants	4 (21.1%)
CTC1	3 (75%)
ACD	1 (25%)
Age at diagnosis (years)	
First visit	4.1 (0.1-23.8)
Initial diagnosis of FEVR/TBD	5.7 (0.3-36.7)
Male	15 (79.8%)
Female	4 (21.1%)
ROP ≥32 weeks	8 (42.1%)
ROP <32 weeks	11 (57.9%)

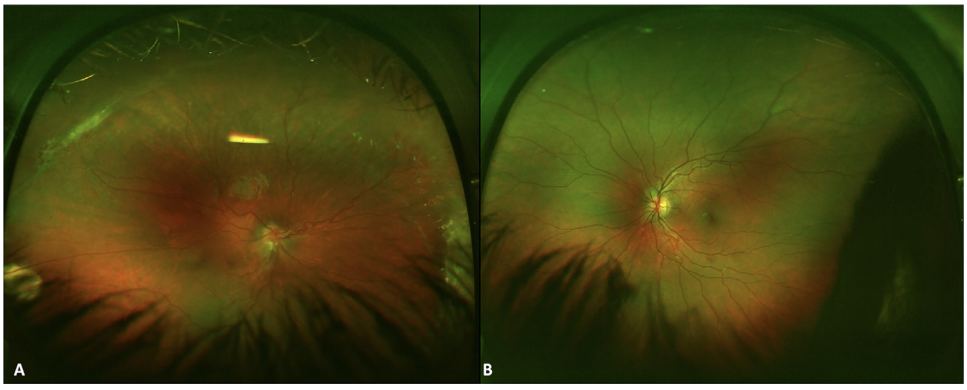

FIGURE 1. Fundus photographs of the right and left eye (A and B), from an ex-24-week-old male with *LRP5* variant diagnosed as atypical ROP with tortuous vessels, incomplete peripheral vascularization, dragging of the macula, exudation temporally and retinal detachment in the periphery in the OD and tortuous vessels and incomplete peripheral vascularization in the OS.

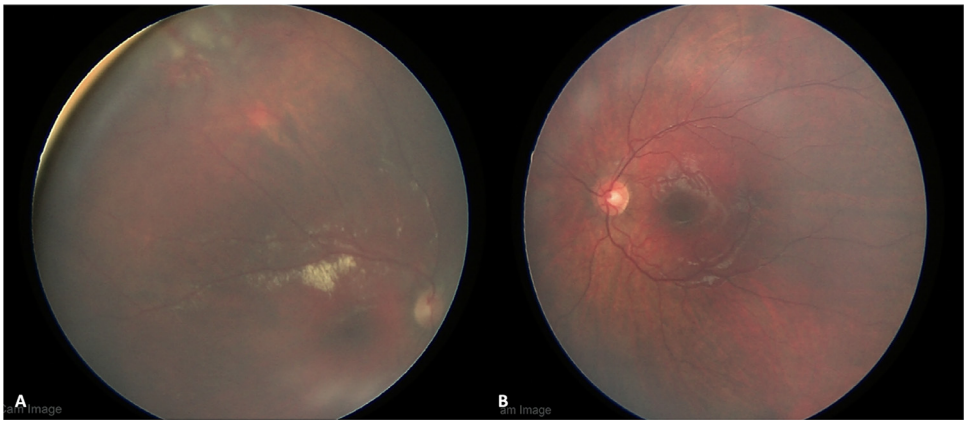

FIGURE 2. Fundus photographs of the right and left eye (A and B), from an ex-31-week-old male with *FZD4* variant diagnosed as atypical ROP with temporal exudation, tortuous vessels, telangiectatic vessels, and incomplete peripheral vascularization in the OD and tortuous vessels and incomplete peripheral vascularization in the OS.

TABLE 2. Demographic Information, Genetic Variant, and Fundoscopy Findings in Patients With Atypical ROP During Examination Under Anesthesia

Gene	Patient	Genetic variant	Gestational age (weeks)	Eye	Fundoscopy findings	Treatment
LRP5	1	Heterogyzous c.60G>A (Silent)	24	OD	Incomplete peripheral vascularization, tortuous vessels	Laser photocoagulation and STK
				OS	Incomplete peripheral vascularization, tortuous vessels, funnel retinal detachment	Laser photocoagulation, IVB, and STK
	2	Heterogyzous c.2324T>C (p.Ile775Thr)	25	OD	Incomplete peripheral vascularization, tortuous vessels, neovascularization, vitreous hemorrhage	IVB
				OS	Incomplete peripheral vascularization, tortuous vessels, neovascularization, vitreous hemorrhage	IVB
	3	Heterogyzous c.1528C>G (p.Leu510Val)	25	OD	Incomplete peripheral vascularization, neovascularization	Laser photocoagulation, IVB, and STK
				OS	Incomplete peripheral vascularization, neovascularization	Laser photocoagulation, IVB, and STK
	4	Heterogyzous c.1331G>A (p.Arg444His)	23	OD	Incomplete peripheral vascularization, tortuous vessels, neovascularization, exudation, fovea plana	Laser photocoagulation, IVB, and STK
				OS	Incomplete peripheral vascularization, tortuous vessels, neovascularization, fovea plana	Laser photocoagulation, IVB, and STK
	5	Heterogyzous c.1912A>G (p.Lys638Glu) c.4066G>A (p.Asp1356Asn)	34	OD	Incomplete peripheral vascularization, tortuous vessels, retinal detachment, exudation, dragging	Laser photocoagulation, IVB, and STK
				OS	Incomplete peripheral vascularization, tortuous vessels	Observation
FZD4	6	Heterogyzous c.1010A>G (p.His337Arg)	26	OD	Incomplete peripheral vascularization, dragging	Laser photocoagulation
				OS	Incomplete peripheral vascularization, retinal detachment	Laser photocoagulation and pars plana vitrectomy
	7	Heterogyzous Deletion (Entire coding sequence)	32	OD	Incomplete peripheral vascularization, straightening of vessels	IVB
				OS	Incomplete peripheral vascularization, exudation, dragging	IVB and STK
	8	Heterogyzous c.1441A>C (p.Ile481Leu)	31	OD	Incomplete peripheral vascularization, tortuous vessels, exudation, telangiectatic vessels	Laser photocoagulation, IVB, and STK
				OS	Incomplete peripheral vascularization, tortuous vessels	Observation
TSPAN12	9	Heterogyzous c.469-3C>T (Intronic)	26	OD	Incomplete peripheral vascularization, retinal detachment, exudation, telangiectatic vessels, fovea plana	Laser photocoagulation and STK
				OS	Incomplete peripheral vascularization, retinal detachment	Observation
	10	Heterogyzous c.695T>C (p.Val232Ala); c.763C>G (p.Pro255Ala)	32	OD	Retinal detachment	Observation
				OS	Retinal detachment	Observation

(*continued on next page*)

TABLE 2. (*continued*)

Gene	Patient	Genetic variant	Gestational age (weeks)	Eye	Fundoscopy findings	Treatment
CTNNA1	11	Heterogyzous c.1636C>T (p.Arg546*); c.795C>G (p.Asp265Glu)	28	OD	Incomplete peripheral vascularization, dragging	Laser photocoagulation, IVB, STK and pars plana vitrectomy
				OS	Incomplete peripheral vascularization	Laser photocoagulation and STK
	12	Heterogyzous c.608A>C (p.His203Pro)	37	OD	Incomplete peripheral vascularization, coloboma	Observation
				OS	Incomplete peripheral vascularization, patches of hyperpigmentary change	Observation
KIF11	13	Heterogyzous c.957C>G (p.Ile319Met)	27	OD	Incomplete peripheral vascularization, neovascularization	Laser photocoagulation, IVB, and STK
				OS	Incomplete peripheral vascularization, neovascularization	Laser photocoagulation, IVB, and STK
NDP	14	Hemizygous c.188C>T (p.Ala63Val)	36	OD	Retinal detachment	Observation
				OS	Retinal detachment	Observation
ZNF408	15	Heterogyzous c.1307C>T (p.Pro436Leu)	34	OD	Incomplete peripheral vascularization, tortuous vessels, neovascularization	Laser photocoagulation and IVB
				OS	Incomplete peripheral vascularization, tortuous vessels, neovascularization	Laser photocoagulation and IVB
CTC1	16	Heterogyzous c.2954_2956del (p.Cys985del) c.859C>T (p.Arg287)	34	OD	Incomplete peripheral vascularization, terminal arborization of vascular branches, aneurysmal dilation of arterioles	Laser photocoagulation and IVB
				OS	Incomplete peripheral vascularization	Laser photocoagulation and IVB
	17	Heterogyzous c.2758+ G > *T* c.2954 2956del (p.Cys985del)	27	OD	Incomplete peripheral vascularization, tortuous vessels, scattered hemorrhages	Laser photocoagulation, IVB, and STK
				OS	Incomplete peripheral vascularization, tortuous vessels, vitreous hemorrhage	Laser photocoagulation, IVB, and STK
	18	Heterogyzous c.2518C>T (p.Arg840Trp) c.2888C>G (p.Pro963Arg)	34	OD	Incomplete peripheral vascularization	Laser photocoagulation, and IVB
				OS	Incomplete peripheral vascularization, exudation, telangiectatic vessels	Laser photocoagulation, IVB and STK
ACD	19	Heterogyzous c.1220C>T (p.Ser407Leu)	24	OD	Incomplete peripheral vascularization, tortuous vessels	Laser photocoagulation, IVB, and STK
				OS	Incomplete peripheral vascularization, tortuous vessels	Laser photocoagulation, IVB, and STK

infant ages. Meaning that over time, retinal vessels grow to fully encompass all areas of the peripheral retina. However, FEVR, as a disease, tends to be inert or progress as the infant ages. Meaning that over time, retinal vessels remain abnormal and peripheral avascularity persists, eventually leading to possible leakage and RD.

ROP and TBDs are also classified as distinct diseases. However, TBDs are associated with IURG[7] and share overlapping clinical features with ROP, such as retinal avascularity and neovascularization.[8,10-12] Differentiating TBDs from ROP becomes more straightforward when systemic features are present. Syndromic manifestations of TBDs in-

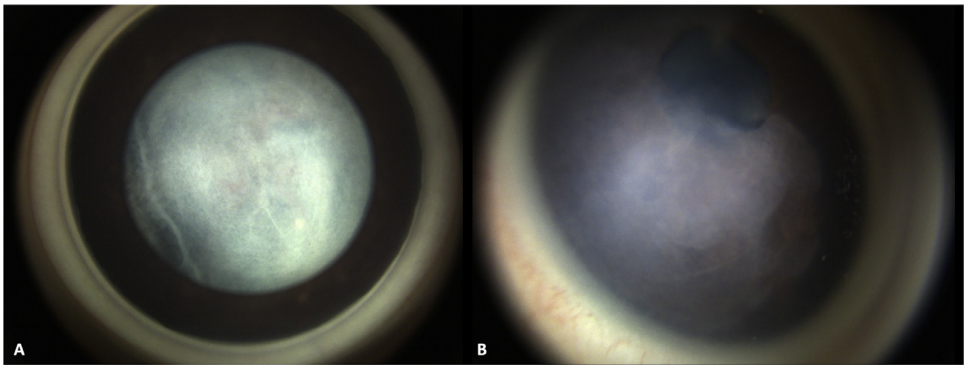

FIGURE 3. Fundus photographs of the right and left eye (A and B), from a 32-week-old male with *TSPAN12* variant diagnosed as atypical ROP with retinal detachment in both eyes.

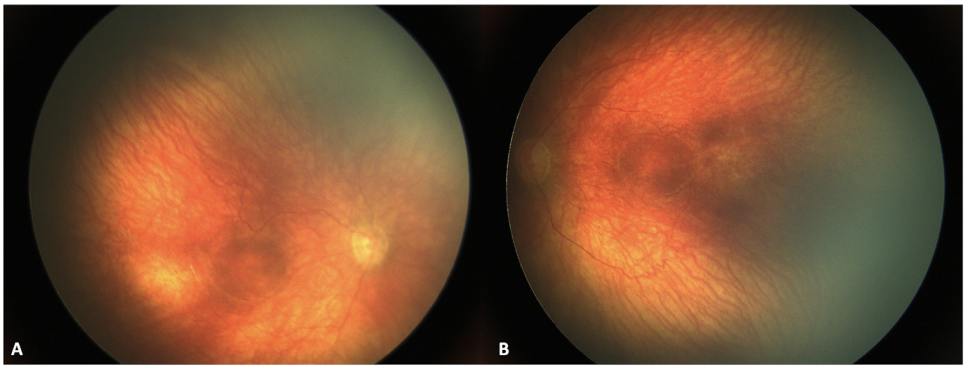

FIGURE 4. Fundus photographs of the right and left eye (A and B), from a 24-week-old male with *ACD* variant diagnosed as atypical ROP with incomplete peripheral vascularization and tortuous vessels in both eyes.

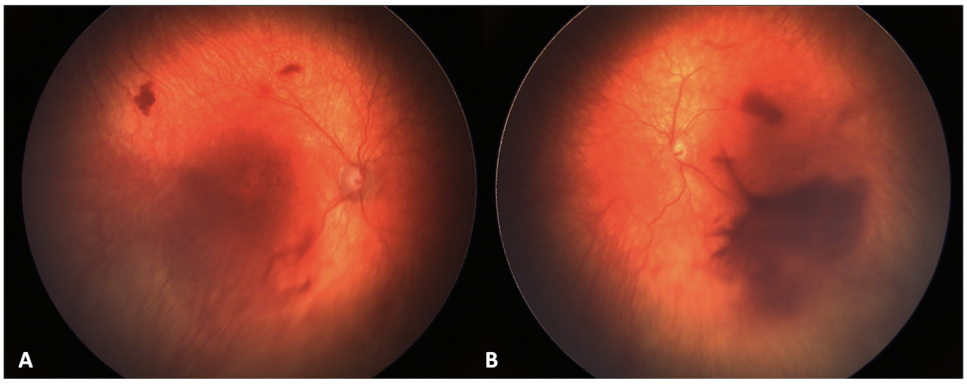

FIGURE 5. Fundus photographs of the right and left eye (A and B), from a 27-week-old male with *CTC-1* variant diagnosed as atypical ROP with incomplete peripheral vascularization, tortuous vessels and scattered hemorrhages in the OD and vitreous hemorrhage in the OS.

clude dyskeratosis congenita (DC),[6] Hoyeraal-Hreidarsson syndrome, Revesz syndrome, and Coats plus syndrome.[5,6] Notably, TBDs can also present asymptomatically. In the absence of systemic features, specific findings on FA can aid in distinguishing TBDs. A recent study highlighted that vascular changes in TBDs are not limited to the periphery and, in some cases, extend to zone 1. Patients frequently exhibited incomplete peripheral vascularization, with most demonstrating aneurysmal dilatation (85.7%), terminal arborization (85.7%), and anastomotic loops (85.7%) and some with capillary dropout.[13]

Studies have examined the incidence of genetic variants in the Norrin/beta-catenin pathway such as *FZD4*, *LRP5*, *NDP*, known to be implicated in FEVR, in patients with ROP.[14] Many of these studies have identified a higher incidence of genetic variant in patients with severe ROP.[15-21] A study on *FZD4* variants in patients with FEVR and ROP found that 3 of 4 patients with ROP demonstrated progression to severe disease and ultimately poor outcomes.[22] The presence of genetic variants associated with FEVR in cases of advanced ROP, in addition to the similarities in clinical presentations between the 2 conditions, points to a possible overlap of disease due to genetic factors.[23]

A molecular pathway implicated in retinal vasculopathies, such as FEVR and ROP, may also underlie shared clinical features of patients with TBD. Several studies have established a bidirectional relationship between telomere biology and the Wnt signaling pathway.[24,25] Mice deficient in Wnt signaling have shorter telomeres and reduced telomerase activity.[26] Gene expression analysis in induced pluripotent stem cells (iPSCs) from DC patients has revealed decreased Wnt signaling.[27] In a human intestinal organotypic model of DC generated from patient iPSCs, treatment with Wnt agonists ameliorated telomere shortening and rescued the intestinal DC phenotype.[28]

The combination of these studies on overlapping genetic pathophysiology of FEVR, ROP, and TBD and our observations of shared clinical features among our cohort's patients warrant additional preclinical studies to identify exact overlapping genetic pathophysiology.

Regarding management of FEVR, ROP, and TBD, options include anti-VEGF therapy to address neovascularization and leakage, peripheral laser photocoagulation treatment for vascular non-perfusion, and surgical repair of RD.[8,29-33] Decisions are often made in a case-by-case basis depending on the spectrum and phenotype of the disease. Our results showed that final VA was worse than 20/200 in 42.3% of treated eyes, indicating that even with appropriate treatment, vision can worsen. Also, late presentation with exudative or tractional RD or vitreous hemorrhage indicates poor prognosis.[34,35] Currently, there is no effective treatment for TBD except symptomatic care for its systemic manifestations.[33]

In our experience, patients with ROPER and ROPMERE may present with unpredictable activation episodes followed by inactive stages. Recent advances in imaging of infants with wide-field photography and angiography have tremendously increased our understanding of retinal vascular diseases and can help guide management.[4,13,36] Early and correct diagnosis of ROPER and ROPMERE is important in distinguishing them from ROP, which once treated or regressed does not characteristically progress. These infants need to be closely monitored for progression of disease early and often in their life, including with serial angiography. Areas of abnormal vasculature with leakage should be considered needing to be treated with solely laser photocoagulation or with a combination of anti-VEGF therapy and laser photocoagulation.[9,23]

For patients with ROPMERE, early diagnosis is essential to ensure that genetic counseling, annual cancer screenings, and symptom-specific treatment are provided.[36,37] Patients can go undiagnosed until later in life due to the lack of awareness of disease. If a patient diagnosed with ROP exhibits features such as early-onset RD, features of mixed exudative and ischemic retinopathy, bilateral Coats-like disease, retinal disease being more severe than expected for gestational age, poor response to treatment, or recurrence, the diagnosis should be reassessed, and suspicion of TBD should prompt genetic testing. Also, systemic evaluation should be conducted and the guidelines may vary based on diagnosis.

Limitations to our study exist, specially due to the sample size. Functional assays to discern causality more definitively are warranted in future studies as underlying genetic susceptibility to ROP and genetic similarities between ROP, FEVR, and TBD point to a clinical spectrum between these entities.

This study suggests that the presence of disease-causing variants associated with FEVR or TBD may exacerbate peripheral retinal ischemia leading to a more aggressive or advanced presentation of ROP. Clinicians should maintain a high index of suspicion of and perform genetic testing for ROPER and ROPMERE in severe or unusual presentations of ROP, or when the disease does not evolve as expected. Although more cases are likely to be identified as genetic analysis becomes more accessible, further studies are needed to identify the overall prevalence of FEVR and TBD variants in patients diagnosed with ROP. Disease in these patients may display complex and unpredictable behavior, and close follow-up is required for improved outcomes.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

NATASHA F.S. DA CRUZ: Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **JULIA L. HUDSON:** Writing – review & editing, Methodology, Investigation, Formal analysis. **JESSE D. SENGILLO:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **SERENA M. SHAH:** Writing – review & editing, Methodology, Investigation. **FRANCISCO LOPEZ-FONT:** Writing – review & editing, Methodology, Formal analysis. **CATHERIN I. NEGRON:** Validation, Supervision. **MICHEL E. FARAH:** Writing – review & editing, Visualization, Validation, Formal analysis. **AUDINA M. BERROCAL:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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