Available online at www.sciencedirect.com**ScienceDirect**journal homepage: www.elsevier.com/locate/survophthal**Review article****Macular neovascularization in inherited retinal diseases: A review**

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ABSTRACT

Inherited retinal diseases (IRDs) are the most common cause of blindness in working-age adults. Macular neovascularization (MNV) may be a presenting feature or occurs as a late-stage complication in several IRDs. We performed an extensive literature review on MNV associated with IRDs. MNV is a well-known complication of Sorsby fundus dystrophy and pseudoxanthoma elasticum. Those with late-onset Stargardt disease may masquerade as exudative age-related macular degeneration (AMD) when MNV is the presenting feature. Peripherinopathies may develop MNV that responds well to a short course of anti-vascular endothelial growth factor (anti-VEGF) therapy, while bestrophinopathies tend to develop MNV in the early stages of the disease without vision loss. Enhanced S-cone syndrome manifests type 3 MNV that typically regresses into a subfoveal fibrotic nodule. MNV is only a rare complication in chorioideraemia and rod-cone dystrophies. Most IRD-related MNVs exhibit a favorable visual prognosis requiring less intensive regimens of anti-vascular endothelial growth factor therapy compared to age-related macular degeneration. We discuss the role of key imaging modalities in the diagnosis of MNV across a wide spectrum of IRDs and highlight the gaps in our knowledge with respect to the natural history and prognosis to pave the way for future directions of research.

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1. Overview

Inherited retinal diseases (IRDs) comprise a heterogeneous group of monogenic diseases exhibiting autosomal dominant or recessive, X-linked, and mitochondrial inheritance patterns. Despite the approval of voretigene neparvovec-rzyl (Luxturna™), for an extremely rare form of RPE65-associated retinopathy, this group of diseases remains the most common cause of blindness in working-age adults.^{67,102} Sight-threatening complications, such as cystoid macular edema, foveoschisis, macular hole, macular pucker, vitelliform lesions, foveal atrophy, and macular neovascularization (MNV), occur across a spectrum of IRDs. The widespread availability of anti-vascular endothelial growth factor (anti-VEGF) agents has led to their frequent use in IRD-related MNV, often with little or no level III evidence of efficacy.^{15,143} It is imperative that we understand the natural history of IRD-related MNV to avoid overtreatment, as these lesions may be stable for long periods after a short course of anti-VEGF therapy, in contrast to those associated with age-related macular degeneration (AMD). To date, IRD-related MNV has mostly been described in case series¹¹¹ with variable use of multimodal imaging to describe the size and nature of the vascular network. In a series of 8 IRD-related MNV cases, followed for 6–148 months, Marano and coworkers¹¹¹ emphasized their favorable visual prognosis without treatment. This cannot be generalized to all IRDs, given that it was published prior to the widespread safe and efficacious use of anti-VEGF therapy. The authors described the natural history of MNVs associated with Best vitelliform dystrophy, pattern dystrophies, gyrate atrophy (GA), and retinitis pigmentosa (RP) in which the MNV lesion generally underwent spontaneous regression to a small, focal fibrotic scar resulting in only mild visual impairment. Nevertheless, these findings mirrored prior observations of MNV associated with fundus flavimaculatus,^{26,89,100} reticular dystrophy,^{113,181} and pattern dystrophy.^{28,110} With the advent of multimodal imaging in recent years to phenotype IRDs,^{52,64,128} it is timely to review the literature on IRD-related MNV to facilitate an accurate diagnosis and an understanding of the role of observation or anti-VEGF therapy. This review is divided into 3 sections focusing on IRDs with (1) drusen-like lesions resembling AMD; (2) centrifugal progression often characterized by macular flecks, vitelliform deposits, or other patterns of pigmentation; and (3) those with centripetal progression characterized by early widespread retinal involvement, encroaching into the macula in the late stages. In this review, the consensus nomenclature for reporting neovascular AMD will be adopted for describing IRD-related MNV.¹⁷⁷ For each condition, a brief description of the clinical features is followed by the MNV imaging characteristics, treatment options, and outcomes.

2. Drusen-like lesions resembling AMD

Three rare dominant IRDs share causative genes that are integral to extracellular matrix integrity. These are often considered phenocopies of AMD due to their characteristic subretinal deposits resembling reticular pseudodrusen and soft drusen.

Sorsby fundus dystrophy (SFD, MIM#136900) is a fully penetrant macular disease with systemic associations due to

pathogenic sequence variants in TIMP3 (MIM#188826) located on chromosome 22q12.3.¹⁸⁹ TIMP3 encodes the third of a 4-member family of tissue inhibitor metalloproteinases. A total of 18 distinct sequence variants in TIMP3 have been identified with most being missense mutations in the C-terminal domain (exon 5) except for p.(Ser38Cys), the truncating variant p.(Glu139 *), and the splice variant c.439-2dupA.^{98,131}

Doyne honeycomb retinal dystrophy (DHRD, MIM#126600), also known as malattia leventinese or familial dominant drusen, is another fully penetrant disease due to a single variant p.(Arg345Trp) in the EFEMP1 (MIM#601548) gene located on chromosome 2p16.1,¹⁷⁹ coding the third of a family of 6 extracellular matrix glycoproteins (Fibulin 3).

Late-onset retinal degeneration (LORD, MIM#605670) is a fully penetrant Bruch membrane disease due to pathogenic sequence variants in C1QTNF5 (MIM#608752) located on chromosome 11q23.3,⁶³ a secreted and membrane-associated protein responsible for adhesion between the retinal pigment epithelial cells and the retinal pigment epithelium (RPE) layer and the Bruch membrane. To date, 6 amino acid substitutions at positions, 163, 180, 186, 188, 190, and 216, have been associated with LORD or GA-like choroidal dystrophy.^{25,82,178} The p.(Ser163Arg) is the most common founder mutation encountered.⁹⁶ Variable phenotypes have been reported between these variants, which may account for differences in the risk of MNV formation.^{193,194} Fig. 1 demonstrates the unique clinical phenotypes of these 3 AMD masquerades.

2.1. SFD

SFD presents in the fourth decade to the fifth decade with a visual impairment from MNV or macular atrophy.¹⁷³ Clinically, patients often report impaired vision in low lighting with central scotomas or peripheral visual field defects related to expanding geographic atrophy, MNV, or both. On multimodal imaging, reticular pseudodrusen⁵⁶ are frequently observed in the sixth decade of life, progressing to diffuse elevation of the retinal pigment epithelium (RPE) from Bruch membrane.⁸³

MNV is found in over 60% of SFD, and most have bilateral sequential lesions separated by a median onset of 3 years.^{12,170} MNV may be type 1, type 2, or a variant of polypoidal choroidal vascularization in the mid-periphery.^{22,36,57,91} Optical coherence tomography (OCT) and OCT angiography (OCTA) have been used to noninvasively demonstrate MNV and its regression after treatment in SFD.¹²⁶ Although the underlying pathophysiology of TIMP3 mutations remains unknown, animal and *in vitro* studies have suggested both gain and loss of function resulting in altered TIMP3 turnover and reduced metalloproteinase inhibitory activity. Downstream effects of altered TIMP3 function may include increased VEGF binding to VEGF receptor 2^{74,151} and the loss of inhibition of 2 enzymes, disintegrin and metalloproteinase 17 (ADAM17), which facilitate the release of tumor necrosis factor alpha, resulting in proinflammatory and proangiogenic effects.¹⁷¹ This may explain the high risk of MNV and the potential extraocular associations in SFD.^{105,118}

Argon laser, photodynamic therapy (PDT), steroids, anti-VEGF agents, and anti-tumor necrosis factor alpha biologics have been described as treatments (Table 1). The initial 2 have

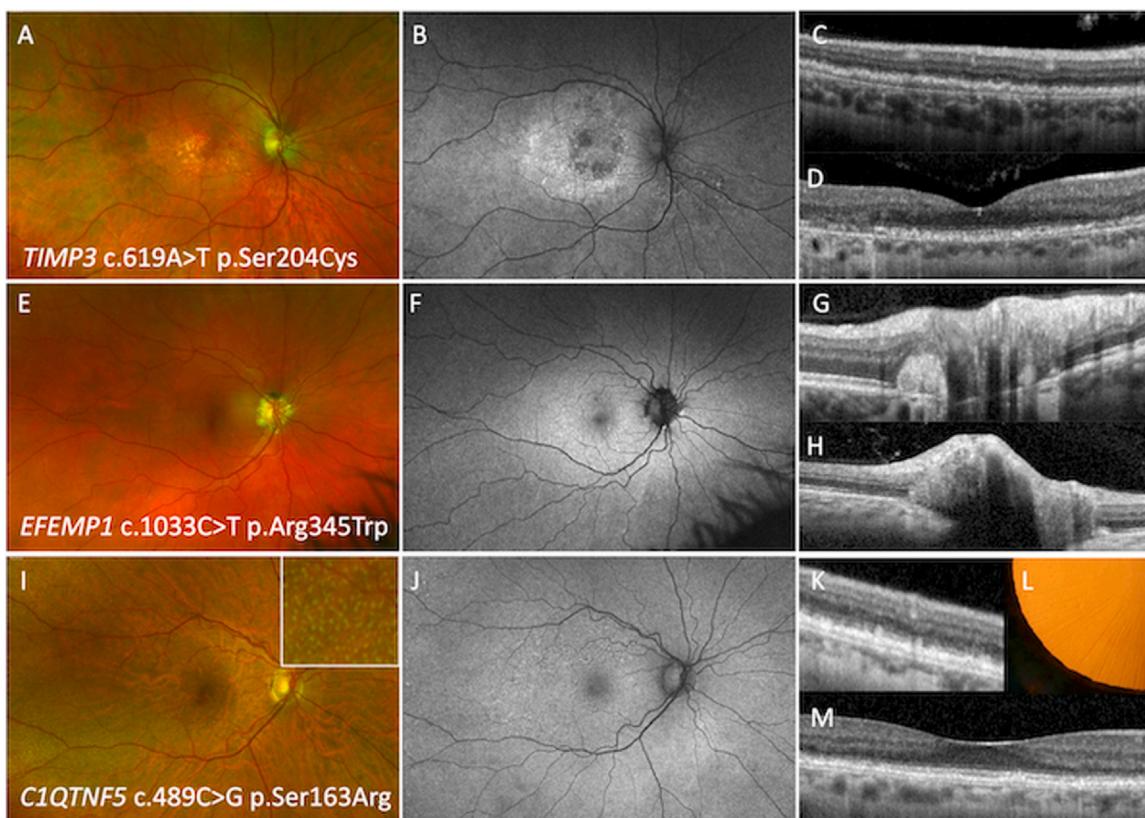


Fig. 1 – Illustrative cases of Sorsby fundus dystrophy (SFD) (A–D), Doyne honeycomb retinal dystrophy (DHRD) (E–H), and late-onset retinal degeneration (I–M). Optos imaging of a 47-year-old male with nyctalopia and scotomas showed parafoveal atrophy (A) and speckled hyperautofluorescence surrounding central hypoautofluorescent patches (B). Optical coherence tomography (OCT) showed diffuse and irregular elevation of the retinal pigment epithelium (RPE) secondary to Bruch's membrane-RPE separation in the parafoveal (C) and foveal regions (D). SFD was suspected and confirmed with a pathogenic TIMP3 variant identified. Optos imaging of an asymptomatic 51-year-old male showed small macular drusen and drusen at the disc margin (E), which were hyperautofluorescent (F). OCT showed a nodular elevation of the RPE at the site of the disc margin (G), which must be distinguished from peripapillary hyperreflective ovoid mass-like structures (PHOMSS) that are hyperreflective lateral bulges from distended axons due to axoplasmic stasis and resides above the RPE (H). Genetic analysis confirmed DHRD due to the known EFEMP1 mutation. Optos imaging of a 61-year-old female with nyctalopia showed peripheral white dots (I, inset) and speckled hyperautofluorescence in the macular region (J). OCT showed subretinal discrete deposits corresponding to the white dots and diffuse elevation of the RPE (K). Anterior zonules were long (L), and there was diffuse thickening of the Bruch membrane (M). Genetic analysis confirmed late-onset retinal degeneration due to a C1QTNF5 mutation.

now been abandoned in favor of anti-VEGF agents due to their poor visual outcomes.^{12,170} Sivaprasad and coworkers^{12,170} hypothesized that the abnormal RPE-Bruch membrane complex may accelerate recurrent MNV formation following laser, and the thickened Bruch membrane may limit penetration of PDT. They noted a short-term (6 month) benefit in combining juxtascleral depot administration of anecortave, an anti-angiogenic analog of cortisol acetate, with an intravitreal anti-VEGF agent.^{12,170} Others have also noted limited benefit from PDT.^{145,191} The long-term data (> 5 years) on bevacizumab and ranibizumab have demonstrated safety and efficacy although intraocular inflammation has been associated with the off-label use of bevacizumab.^{11,12,47,50,58,78,79,81,117,126,185} There remains no consensus on dosing regimens despite a treat and extend

protocol being advocated by Kaye and coworkers⁷⁹ and Tsokolas and coworkers.¹⁸⁵ Conversely, Gliem and coworkers⁵⁷ and Baston and coworkers¹² recommended monthly monitoring and *pro re nata* injection to reduce the treatment burden. Spaide¹⁷⁶ recently reported the use of subcutaneous adalimumab (an inhibitor of tumor necrosis factor alpha), as a molecularly targeted approach. He described a 35-year-old woman with bilateral aggressive MNV initially treated with intravitreal 4-mg triamcinolone and later bevacizumab. Over a follow-up period of 18 months, there were no signs of disease activity once the patient was switched to adalimumab.¹⁷⁶ Further investigations into the use of other anti-tumor necrosis factor alpha agents, such as etanercept, infliximab, certolizumab pegol, and golimumab, are now warranted.

Table 1 – Summary of Treatment Outcomes in Drusen-like Lesions Resembling Age-related Macular Degeneration.

Disease	Author	Treatment	Demographics at Onset of MNV (Case #)	Baseline VA	Final VA	Follow-Up Duration	Comments
Sorsby Fundus Dystrophy	Gemenetzi et al. ⁵⁰	Bevacizumab OD (6) PDT + Bevacizumab OS (3)	34 F OD → OS 44 F OD only	20/200 (OD) 20/20 (OS) 20/200 (OD)	20/160 (OD) 20/20 (CS) 20/20 (OD)	33 m 12 w	p.Ser204Cys. Onset separated by 3 years between 2 eyes. p.Ser204Cys
	Gray et al. ⁵⁸	Bevacizumab OS (3)	38 F OS only	20/20 (OS)	20/20 (CS)	14 m	p.Ser181Cys. Extrafoveal MNV
	Balaskas et al. ¹¹	PDT OS Ranibizumab OD (14)	41 M OS → OD 44 M OD	6/18 (OS) 6/5 (OD) 20/40 (OD)	6/60 (OS) 6/15 (OD) 20/25 (OD)	4 y	p.Ser204Cys. MNV developed in fellow eye 2 years after first eye. p.Tyr159Cys
	Fung et al. ⁴⁷	PDT + Bevacizumab OD (6)				4 y	
	Gliem et al. ⁵⁷	Bevacizumab OS (35)	45 M (VI.5) OD	20/20 (OD)	20/20 (OD)	6 y	p.Tyr182Cys. Pro re nata regime.
		Bevacizumab OS (1)	54 (III.4) OS	20/25 (OS)	20/20 (CS)	12 m	p.Ser204Cys.
		Bevacizumab OU (2)	56 (III.8) OS → OD	20/32 (OS)	20/20 (CS)	8 m	p.Ser204Cys. Fellow eye developed PCV nasal to disc.
	Keller et al. ⁸¹	PDT + Ranibizumab OS (3)	32 M OS → OD	NR (OU)	CF (OS) 20/30 (OD)	5 y	PDT followed by 3 doses of ranibizumab in OS and 7 recurrences of MNV in OD.
		Ranibizumab	28 M OS	20/200 (OS) NR (OD)	20/50 (OS) 20/200 (OD)	4 y	26 recurrences of MNV between OU, all treated with ranibizumab Subfoveal scar.
	Mohla et al. ¹²⁶	Bevacizumab (2)	52 F OD	20/200 (OD)	20/60 (OD)	7 m	p.Ser204Cys. 4 weeks apart.
	Menassa et al. ¹¹⁷	Ranibizumab (6 OD, 5 OS)	38 M OS → OD	20/200 (OS) 20/20 (OD)	20/200 (OS) 20/25 (OD)	5 y	p.Ser204Cys. MNV developed in OD 5 years later.
	Tsokolas et al. ¹⁸⁵	Bevacizumab (24 OD, 42 OS)	34 F OD → OS	NR (OU)	20/400 (OD)	20/40 (OS)	p.Ser204Cys. Prior PDT in OS.
		Bevacizumab (5 OD, 79 OS)	36 F OD → OS	20/25 (OD)	20/200 (OD)	6 y	p.Ser204Cys
		Surgical excision OS	34 M OS	20/20 (OS) 20/100 (OS)	20/120 (OS) 20/20 (OS)	2 m	No fluorescein leakage on follow-up.
Doyne Honeycomb Retinal Dystrophy	Pager et al. ¹³⁸						
	Ladas et al. ⁸²	Focal laser OD	45 M OD	20/800 (OD)	20/20 (OD)	3 y	ICG-guided argon green laser on parapapillary and perifoveal polypoidal lesions.
	Dantas et al. ³⁹	Observation OD PDT OS	39 F OD → OS	20/800 (OD) 20/25 (OS)	20/800 (OD) 20/60 (OS)	5 y	Type 2 MNV in OD progressed to subretinal fibrosis
	Sohn et al. ¹⁷²	Bevacizumab OS	56 F OS only	20/250 (OS)	20/50 (CS)	1 y	OS VA dropped to 20/60 with SRF due to type 2 MNV.
		Bevacizumab OS	39 F OS only	20/200 (OS)	20/20 (CS)	2 y	Type 1 MNV, 2 doses given.
		Observation OD	41 M OD only	20/20 (OD)	20/120 (OD)	6 y	Type 1 MNV, 7 doses given.
							Type 1 MNV evolved into disciform scar.

(continued on next page)

Table 1 – (continued)

Disease	Author	Treatment	Demographics at Onset of MNV (Case #)	Baseline VA	Final VA	Follow-Up Duration	Comments
	Patel et al. ¹⁴⁴	Bevacizumab OS (5)	65 F OS only	20/200 (OS)	20/400 (OS)	4 m	Monthly interval with no change in MNV area on OCTA.
	Enomoto et al. ⁴²	Bevacizumab OS (20) Ranibizumab OD (2)	41 M OS → OD	20/40 (OS)	20/200 (OS)	15 y	Pro re nata regime.
	Sheyanth et al. ¹⁶⁹	Aflibercept OU (3)	67 F OU	20/20 (OD)	NR (OS)		Monthly interval with no change in angiography leakage.
Late-Onset Retinal Degeneration	Ayyagari et al. ⁹	Focal laser OS Observation OD Focal laser OS	58 F (IV-11) OS → OD 64 F (IV-8) OS only	20/100 (OD) 20/30 (OS)	20/100 (OD) 20/30 (OS)	3 m	Recurrence adjacent to treated area eventually became subfoveal.
	Mandal & Lotery ¹⁰⁹	Ranibizumab OS Bevacizumab OD	54 F OS → OD	20/20 (OD)	CF (OD)	3 y	Recurrence at margin 3 months later.
	Keenan et al. ⁸⁰	Observation OU	57 F (V-33) OD → OS	20/200 (OS)	CF (OS)		
		Observation OU	55 M (V-34) OU	6/7.5 (OD) 6/24 (OS)	6/38 (OD) 6/24 (OS)	17 m	p.Ser163Arg Recurrence in both eyes at 17-month follow-up treated with bevacizumab.
		Observation OU	60 F (V-41) OU	NR	NR	8 y	p.Ser163Arg Peripheral MNV with hemorrhage, not treated.
		Observation OU	60 F (V-42) OU	20/20 (OD) 20/20 (OS) 20/500 (OD) 20/32 (OS)	20/20 (OD) 20/20 (OS) NA No FU	4 y	p.Ser163Arg Peripheral MNV seen with ICGA, not treated.
							p.Ser163Arg Peripheral MNV seen with ICGA with no exudation. OD VA loss due to atrophy.
				20/20 (OD) 20/20 (OS)	No FU		p.Ser163Arg Peripheral MNV seen with ICGA with no exudation.

OS = left eye; OD = right eye; OU = both eyes; PDT = photodynamic therapy; PCV = polypoidal choroidal vascularization; OCTA = optical coherence tomography angiography; MNV = macular neovascularization; ICGA = indocyanine green angiography; NR = not reported.

2.2. DHRD

DHRD typically presents in the fourth decade to fifth decade with mild visual impairment that often progresses to severe impairment of acuity (< 20/200) from geographic atrophy or MNV.⁹³ The mutant *EFEMP1* is misfolded and subsequently accumulates within the RPE and between the RPE and Bruch membrane. Although not entirely understood, animal studies have shown increased basal lamina deposits, excessive complement C3 activation, and generalized RPE and choroidal abnormalities, setting the scene for MNV formation.^{45,115,116} Clinically, small white radially orientated drusen are seen in the perimacular region, as described by Vogt originally,^{43,147,187} progressing to the more typical macular drusen that appear in a honeycomb arrangement as described by Doyne.⁴⁰ The pathognomonic hyperautofluorescent disc margin drusen of DHRD¹⁷⁴ are distinct from optic disc drusen or peripapillary hyperreflective ovoid mass-like structures.⁶⁵ Peripapillary hyperreflective ovoid mass-like structures are hyperreflective bulges of axons herniating laterally over the disc margin, secondary to axoplasmic stasis, which rests upon the RPE/basement membrane complex (Fig. 1H). Conversely, optic disc drusen are hyporeflective structures within the optic nerve head that projects a hyperreflective border. In contrast, disc margin drusen are nodular elevations of the RPE adjacent to the Bruch membrane opening (Fig. 1G). The formation of confluent drusen with a honeycomb appearance is also accompanied by a diffuse elevation of the RPE layer.

In a large series of 24 patients from 19 families with DHRD, only 1 developed MNV, whereas the majority lost vision from macular atrophy.¹²⁰ Serra and coworkers¹⁶⁷ compared OCTA features with fundus photography, fluorescein angiography, indocyanine green angiography (ICGA), and OCT in 4 patients with DHRD. They found that OCTA identified flow signals in 3 eyes with exudative MNV, while other multimodal imaging did not demonstrate any leakage.^{45,115,116}

Reports of treatment in DHRD-related MNV remain limited to surgical excision, argon laser, PDT, and anti-VEGF therapy (Table 1). Pager and coworkers described subretinal surgery in a case presenting with acute vision loss due to an active MNV.¹³⁸ Although the surgically excised submacular tissue failed to show histologic evidence of MNV, clinical assessment 2 months after surgery demonstrated restoration of visual acuity from 20/100–20/20 and no evidence of fluorescein leakage on angiography. A case report by Ladas and coworkers⁸² illustrated the unusual coexistence of a polypoidal choroidal vascularization variant of MNV in a patient with DHRD. Here, indocyanine green angiography-guided argon laser was performed on the active peripapillary and perifoveal polypoidal lesions. The authors noted a favorable anatomic and functional outcome 3 years posttreatment with a visual acuity of 20/20 in the treated eye. Dantas and coworkers³⁹ also reported effective treatment with a single PDT application followed for 34 weeks. Sohn and coworkers¹⁷² reported 2 cases of MNV responding to 2 and 7 doses of bevacizumab followed for 15 and 30 months, respectively. Visual acuities in the affected eyes improved from 20/250 to 20/50 and from 20/200 to 20/20, respectively. Enomoto and coworkers reported a case of bilateral sequential MNV

separated by 9 years with a 15-year follow-up.⁴² One eye developed scarring despite 20 bevacizumab injections, while the MNV in the fellow eye was stabilized with only 2 ranibizumab injections over a 5-year period. Patel and coworkers¹⁴⁴ explored the utility of OCTA in IRDs complicated by MNV including a case of DHRD. They found that, after 5 intravitreal bevacizumab injections, the MNV remained largely unchanged with respect to vessel area on OCTA despite a reduction in subretinal fluid (SRF) and continued visual acuity decline over 16 weeks. Sheyanth and coworkers found no change in visual acuity or angiographic leak in a patient receiving bilateral afibercept for MNV after 3 doses.¹⁶⁹ These case report and series illustrated the variable treatment responses in DHRD. Fig. 2 illustrates a case of DHRD-related MNV responding well to anti-VEGF therapy.

2.3. LORD

LORD typically presents with delayed dark adaptation and reduced vision in low lighting during the fifth decade to the sixth decade, accompanied by numerous yellow-white subretinal deposits in the peripheral and perifoveal regions. Central vision is gradually lost by the seventh decade from advancing chorioretinal atrophy through the fovea. Similar to SFD, reticular pseudodrusen are commonly seen in the sixth decade to the seventh decade with spontaneous regression by the eighth decade.²⁴ Despite histopathological evidence of a thickened Bruch membrane,^{63,92,121} spectral domain-OCT has not demonstrated increased RPE elevation with advancing disease.⁸³ A unique anterior segment feature includes the long anterior zonules with peripupillary iris transillumination defects.^{97,180} Borooah and coworkers proposed a staging system (stages 1–3) based on patient age, anterior and posterior segment findings, and the presence of sight-threatening complications such as MNV or atrophy.²³

MNV has been shown to involve both the macular and peripheral retina.^{9,24,109,155} Borooah and coworkers reviewed cases of stage 3 LORD and found several reports of sudden and severe visual decline likely associated with MNV;²³ however, choroidal neovascularization may be asymptomatic and remain peripheral, as demonstrated by Keenan and coworkers using widefield ICG angiography and OCTA.⁸⁰ The mutant protein is thought to act in a dominant negative manner, whereby the wildtype protein is depleted through oligomerization with the mutant protein. Animal models suggest variability in the dominant negative mechanisms amongst different variants.¹⁹³ Therefore, the molecular mechanisms leading to RPE dysfunction, Bruch membrane deposits, and subsequent atrophy and MNV formation remain unclear.^{92,121}

Focal laser and anti-VEGF therapies have been described for the treatment of LORD-related MNV (Table 1). Ayyagari and coworkers described the use of focal laser for MNV in 3 sisters from a dominant pedigree with LORD.⁹ There was a prompt response from 2 separate MNV lesions in the same eye within days of the laser; however, new MNVs developed over subsequent months, at the margins of the treated areas that eventually encroached into the subfoveal region. Notably, even with a low-energy laser setting, there was complete ablation of the RPE and choriocapillaris indicating a

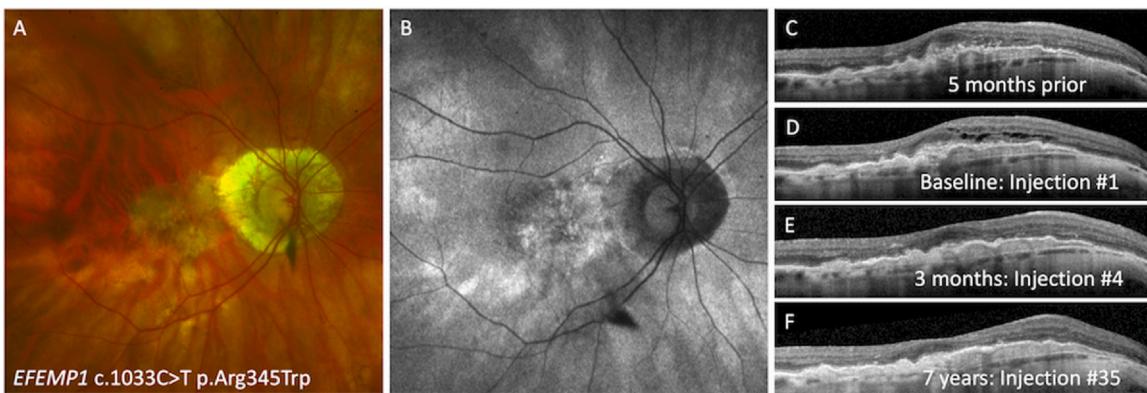


Fig. 2 – Optos pseudocolor and autofluorescence imaging of a 79-year-old female with genetically confirmed Doyne honeycomb retinal dystrophy showing numerous macular drusen and peripapillary atrophy in the right eye (A, B). OCT showed subretinal hyperreflective material and intraretinal cystoid changes consistent with macular neovascularization (C). Visual acuity declined from 6/15–6/60 over a 5-month period of observation with worsening of the cystoid spaces (D). After 3 monthly ranibizumab injections, macular fluid resolved (E). The patient received a total of 35 injections using a treat and extend protocol gradually stretching the interval to 12-weekly with no recurrence of fluid at 7 years (F). Visual acuity declined to 6/38 due to early foveal atrophy.

vulnerability of these layers in LORD. Mandal and Lotery reported anti-VEGF use in LORD-related MNV demonstrating clinical efficacy with a course of 3 monthly injections using ranibizumab and bevacizumab.¹⁰⁹ Although macular fluid resolved promptly, the MNV recurred bilaterally 17 months later.¹⁰⁹ Ganesth and coworkers described a single aflibercept injection in a patient with LORD-related MNV.⁴⁸ Importantly, not all LORD-related MNV requires treatment as some of these are type 1 nonexudative membranes.⁸⁰

3. Centrifugal diseases, including vitelliform and pattern dystrophies

This group of disorders demonstrates a macular predilection with greater cone than the rod system involvement in electrophysiology. The centrifugal IRDs associated with MNV include ABCA4-related retinopathy (MIM#601691) or Stargardt disease, PRPH2-related retinopathy (MIM#179605) or peripherinopathies, BEST1-related retinopathy (MIM#607854) or bestrophinopathies, mutations in DHS6S1, upstream from the PRDM13 gene, (MIM#616842) or North Carolina macular dystrophy, and ABCC6-associated retinopathy (MIM#603234) or angioid streaks complicating pseudoxanthoma elasticum (PXE).

3.1. ABCA4-associated retinopathy or Stargardt disease

Stargardt disease is the most common IRD,¹⁵⁸ accounting for 12% of IRD-related blindness.⁶⁷ Although macular atrophy is the predominant cause of visual loss, there is increasing recognition that MNV can lead to significant visual impairment.^{64,89} Cases of foveal sparing atrophy with subfoveal MNV in late-onset disease may easily be misdiagnosed as AMD due to the resemblance between flecks and drusen on fundus examination.^{69,190}

To date, only a few case reports and series have described the use of laser photocoagulation,⁸⁹ PDT,^{75,86,175} and anti-VEGF therapy^{14,16,152} in patients with phenotypes suggestive of Stargardt disease, albeit some with incomplete genotyping (Table 2). Focal laser is no longer recommended because of collateral damage to the vulnerable RPE. Although the results of PDT were varied, they were, in general, better than the outcomes seen in neovascular AMD. The number of PDT sessions ranged from 1 to 12 with variable visual outcomes from 20/200 to 20/20. Ranibizumab has been reported to be efficacious in reducing macular fluid in some patients with a final VA outcome ranging from 20/400 to 20/30; however, Battaglia Parodi and coworkers¹⁶ raised concerns that VEGF inhibition may accelerate atrophy growth in Stargardt-related MNV due to the vulnerability of the lipofuscin-rich RPE. OCTA studies have shown profound choroidal flow signal voids within the inner choroidal vasculature in Stargardt disease compared to AMD. Rarefaction of the choriocapillaris flow signals also extended beyond RPE atrophy in Stargardt disease.^{1129,157} Thus, studies using OCTA in a genotyped Stargardt disease cohort with MNV are essential to determine the natural history and the role of anti-VEGF therapy. Fig. 3 illustrates a case of Stargardt disease-related MNV responding to anti-VEGF with late visual loss secondary to progressive macular atrophy.

3.2. Pattern dystrophies

Pattern dystrophy is a term used to describe 5 phenotypically distinct disorders, namely, adult-onset foveomacular vitelliform dystrophy, butterfly-shaped pigment dystrophy, reticular dystrophy, multifocal pattern dystrophy simulating Stargardt disease, and fundus pulverulentus. Three of these phenotypes are known to be associated with PRPH2-related retinal dystrophy (peripherinopathies), whereas adult-onset foveomacular vitelliform dystrophy is known to be associated with pathogenic

Table 2 – Summary of Treatment Outcomes in Stargardt Disease and PRPH2-Associated Retinal Disease.

Disease	Author	Treatment	Demographics at Onset of MNV (Case #)	Baseline VA	Final VA	Follow-Up Duration	Comments
Stargardt Disease	Klein et al. ⁸⁹	Xenon photocoagulation (2) Observation	53 F OS only 14 F	20/200 (OS) CF (OS)	20/200 (OS) NR	8 y	Recurrences documented.
	Cheng et al. ³⁵	PDT (2)	OS only 40 F	6/120 (OS)	6/24 (OS)	3 y	No treatment given.
Souied et al. ¹⁷⁵	PDT (1)	OS only 71 F	OD	20/80 (OD)	20/32 (OD)	21 m	Onset during third trimester of pregnancy Sessions 3 months apart.
	PDT (3)	74 F	OD	20/160 (OD)	20/100 (OD)	15 m	
	PDT (2)	70 F	OS	20/63 (OS)	20/50 (OS)	24 m	
Kim et al. ⁸⁷	PDT (12 OD, 2 OS)	41 F OD → OS		20/30 (OD) 20/20 (OS)	20/20 (OD) 20/20 (OS)	31 m	Fellow eye developed MNV at 31 months.
Japiassu et al. ⁷⁵	PDT (2)	53 M OU		20/30 (OD) 20/40 (OS)	20/30 (OD) 20/50 (OS)	6 m	
Battaglia Parodi et al. ¹⁵	Ranibizumab (6 OD, 9 OS)	52 M OU		20/32 (OD) 20/63 (OS)	20/100 (OD) 20/200 (OS)	30 m	Pro re nata regimen.
Battaglia Parodi et al. ¹⁶	Ranibizumab (9)	Case 1		20/60	20/200	24 m	Atrophy enlarged from 5.2 to 7.6 mm ² .
	Ranibizumab (11)	Case 2		20/60	20/30	24 m	Atrophy enlarged from 0.1 to 1.0 mm ² .
	Ranibizumab (14)	Case 3		20/50	20/200	24 m	Atrophy enlarged from 1.7 to 4.1 mm ² .
Querques et al. ¹⁵²	Ranibizumab (3)	26 M OD		20/800 (OD)	20/400 (OD)	6 m	Monthly interval.
Xu et al. ¹⁹²	Ranibizumab (9)	50 M OD		20/20 (OD)	20/20 (OD)	6 y	p.Tyr184*
Bianco et al. ²⁰	Ranibizumab (2)	47 M (IX.1) OD		20/25 (OD)	20/25 (OD)	4 y	Pattern dystrophy with flecks.
Peripherinopathies	Ranibizumab (6)	46 F (X.1) OD		20/20 (OD)	20/20 (OD)	5 y	p.Pro210Ser. Pattern dystrophy with flecks.
Miyata et al. ¹²⁵	Ranibizumab (11) Bevacizumab (2) Pegaptanib (2) Afibercept (19)	56 F OS		20/50 (OS)	20/100 (OS)	8 y	p.Gly137Asp. RP phenotype. PRN treatment regimen for 2 years then switched to bimonthly regimen for 6 years.

OS = left eye; OD = right eye; OU = both eyes; PDT = photodynamic therapy; RP = retinitis pigmentosa; MNV = macular neovascularization; PRN = *pro re nata*. NR = not reported.

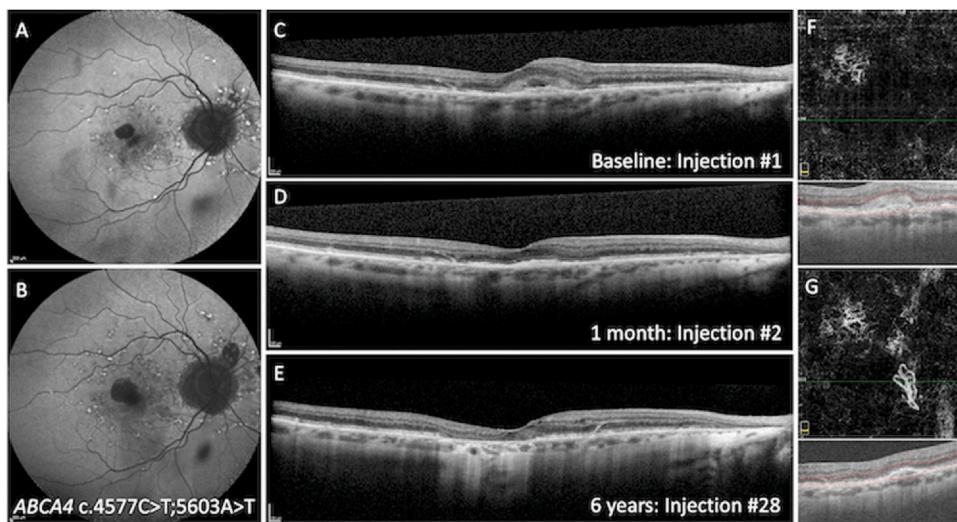


Fig. 3 – Spectralis 55° fundus autofluorescence imaging of an 81-year-old man with genetically confirmed Stargardt disease showing hyperautofluorescent flecks in the macular and peripapillary region (A) and central atrophy that expanded 6 years later to involve the fovea (B). OCT imaging at presentation showed subfoveal type 1 macular neovascularization with subretinal hyperreflective material causing visual decline to 6/30 (C). At 1 month after the first injection, the fluid resolved with improved visual acuity to 6/15 (D). The macula remained dry at 16 weeks. E: OCT scans after a total of 28 injections at 6 years showed no fluid (E). Note that the juxtafoveal atrophy encroaching into the fovea limited the visual acuity to only 6/19. OCT angiography at baseline showed no obvious flow signal at the site of the pigment epithelial detachment (PED) (F). Once fluid resolved, flow signals within the PED were better visualized showing a neovascular network.

variants in BEST1,⁷⁷ IMPG1, and IMPG2.¹¹⁹ Peripherinopathies will be discussed separately below given their variable phenotypes. Butterfly-shaped pigment dystrophy can also be associated with CTNNA1 variants.¹⁶¹ Pattern dystrophy seen with myotonic dystrophy has been associated with MNV.¹⁹⁷ The increasing use of OCT and OCTA has improved the detection of types 1 and 3 MNV in adult-onset foveomacular vitelliform dystrophy^{76,103,144,153,154} by allowing direct visualization of flow signals within the MNV network.¹⁴⁹ A large retrospective case series reported stable visual acuity in adult-onset foveomacular vitelliform dystrophy-related MNV with ranibizumab therapy;¹²³ however, spontaneous resolution of MNV in pattern dystrophy has also been described emphasizing the need for caution when interpreting favorable results in interventional case series.⁵ MNV and its treatment with anti-VEGF therapy have also been reported in cases of North Carolina macular dystrophy¹⁰ and a genetically uncharacterized cone dystrophy.⁶⁰

Peripherinopathy can manifest as butterfly pattern dystrophy, vitelliform macular dystrophy, central areolar choroidal dystrophy, pattern dystrophy simulating fundus flavimaculatus, and RP.⁶⁶ Symptoms and age of onset vary depending on the phenotype with some patients remaining asymptomatic. MNV occurs frequently in peripherinopathy pedigrees affecting 5%–18% of cases.^{85,88,186} Oishi and coworkers¹³⁷ reported 40 Japanese patients from 30 families with PRPH2-associated retinal dystrophy and found MNV in only 2 patients (5%, aged 49 and 55) with an RP phenotype, of which one had concurrent high myopia. Antonelli and coworkers⁷ examined 28 subjects from 11 unrelated families carrying pathogenic heterozygous PRPH2 variants and found MNV in 5

patients (18%) of which extensive chorioretinal atrophy was found in 2, pattern dystrophy in 2, and central areolar choroidal dystrophy in 1. The authors concluded that OCTA was highly informative for MNV detection despite the presence of extensive chorioretinal atrophy.

Single cases of clinically suspected or genetically confirmed that PRPH2-associated retinal dystrophy has illustrated excellent long-term visual outcomes over a 7-year period with a single session of PDT^{17,99} or only a few anti-VEGF injections (Table 2).^{44,99,134,186,192} One of the 2 patients reported by Oishi and coworkers developed bilateral sequential MNV 8 years apart and received > 60 anti-VEGF injections over 13 years.¹³⁷ Despite bilateral anti-VEGF therapy, visual acuity declined to 20/100 and 20/50 due to progressive atrophy.^{125,137} Bianco and coworkers²⁰ reported 2 of 19 patients (11%) aged 46 and 47 years with multifocal pattern dystrophy to exhibit exudative MNV receiving only 6 and 2 anti-VEGF injections, respectively, to maintain a visual acuity of 20/20 and 20/25 over 4–5 years. OCTA may play a role in identifying asymptomatic type 1 MNV⁴⁴ and monitoring for disease recurrence with a *pro re nata* treatment regimen.¹⁹² Phenotypic risk factors for MNV formation in PRPH2 remain unknown as the current literature consists of only a small case series.⁶⁸ Fig. 4 illustrates a case of stable type 1 MNV in PRPH2-related retinal dystrophy after 1 year of anti-VEGF therapy.

3.3. Bestrophinopathies

Dominant and recessive bestrophinopathies exhibit overlapping clinical features¹⁴⁶ including Best vitelliform macular

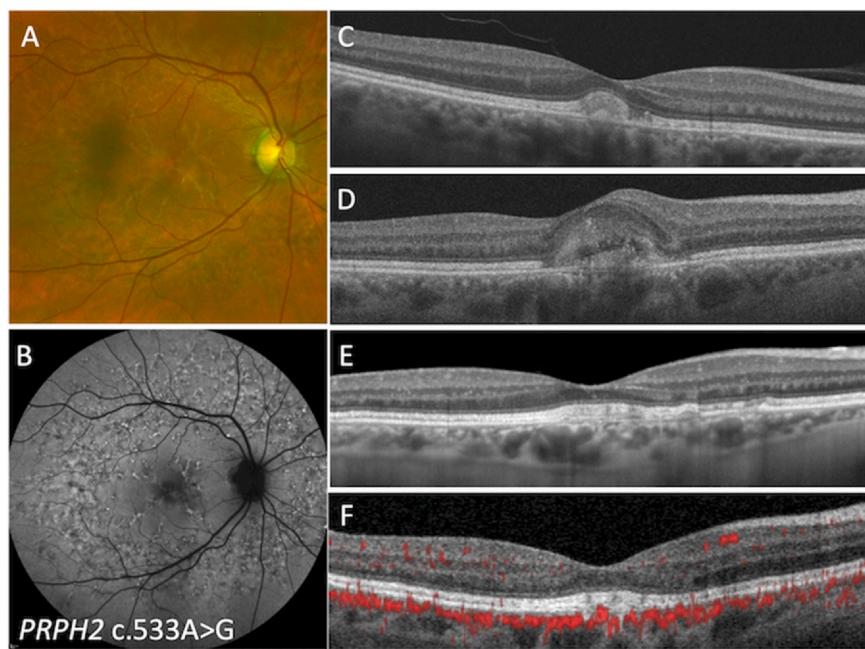


Fig. 4 – Color fundus photo (A) and fundus autofluorescence images (B) of a 63-year-old female with genetically confirmed peripherinopathy showing multifocal pattern dystrophy that simulates fundus flavimaculatus. An OCT scan at age 61 showed an asymptomatic subfoveal vitelliform lesion (C), which remained stable until age 63 when she presented with new onset distortion due to an acute increase in subfoveal hyperreflective material secondary to an exudative macular neovascularization (D). At 1 year, after receiving 10 anti-VEGF injections using a treat and extend regimen, her visual acuity was 6/7.5, and there was no macular fluid at 10 weeks posttreatment (E). Treatment was withheld and visual acuity was maintained at 6/7.5 for the following 4 years after cessation of anti-VEGF therapy. OCT angiography showed a flow signal within the shallow vascularized PED indicating the persistence of the nonexudative type 1 macular neovascularization (F).

dystrophy with multifocal vitelliform lesions, which may be accompanied by 1, 2, or 3 type MNV.^{72,84,124,165,196} These can be exudative (typically in the early stages, 2–3) or non-exudative (usually in the late stages, 4–5).²¹

With clinical examination alone, MNV was found in only 2%–9% of BVMD.^{37,122,127} Using spectral domain-OCT, a larger case series of recessive bestrophinopathies by Kim and coworkers⁸⁷ and Khan and coworkers³¹ showed 10% and 14% of patients, respectively, exhibiting features suspicious of MNV (i.e., pigment epithelial detachment with or without focal choroidal excavation). OCTA has improved the detection of MNV^{144,168} with Guduru and coworkers⁵⁹ reporting 6 of 10 (60%) patients and Battaglia Parodi and coworkers¹⁸ showing that 24 of 66 (36%) eyes had MNV, most observed with stage 4 and 5 lesions. It is now recognized that MNV is no longer confined to stage 6 disease as once proposed.⁴⁹ MNV can be observed in earlier stages potentially altering the natural course of vitelliform lesions.^{38,62} For example, Han and coworkers showed that 63% of eyes with Gass stage 2 vitelliform lesions had OCTA evidence of MNV. A new classification was proposed, whereby MNV may form in stage 2 or 3 in response to impaired choroidal perfusion as demonstrated by Guduru and coworkers in their OCTA study.⁵⁹ Initially, the MNV was covered by intact RPE forming a type 1 configuration with stable visual acuity. Loss of RPE integrity with or without a breakthrough of the MNV (type 2) leads to

reabsorption of the subretinal deposit and collapse of the vitelliform lesion resulting in the visual loss (stage 4). Reversal to stage 2 or 3 with recovery of vision may occur when RPE integrity is restored through spontaneous or anti-VEGF-induced MNV regression. Han and coworkers found 2 structural features to be associated with MNV: subretinal pillars and focal choroidal excavation.⁵⁹

In a retrospective review of 14 eyes from 12 patients (11 with BVMD), Khan and coworkers⁸⁴ reported that MNV was typically active prior to stage 4, developing at a mean age of 15.5 years (range: 6–72). Over a median follow-up period of 2.8 years, they reported a high rate of spontaneous regression of BEST1-related MNV although active treatment with intravitreal bevacizumab was associated with statistically better visual acuity outcomes (logMAR) than observation alone (−0.46 versus 0.17, Table 3). Here, 7 eyes were treated with intravitreal bevacizumab, while 7 eyes underwent observation. Interestingly, most patients only required a single intravitreal injection (median 1, range: 1–10). Similarly, Miyagi and coworkers showed no significant visual gain with ranibizumab in patients with BVMD (Table 3).¹¹⁵

In a retrospective case series of 27 unrelated recessive bestrophinopathy patients, Casalino and coworkers³¹ reported SRF in 75% at presentation with almost 50% of the SRF located within the subfoveal region. Importantly, SRF did not

Table 3 – Summary of Treatment Outcomes Bestrophinopathies and Pseudoxanthoma Elasticum.

Disease	Author	Treatment	Demographics at Onset of MNV (Case #)	Baseline VA	Final VA	Follow-Up	Duration	Comments
Bestrophinopathy	Miyagi et al. ¹¹⁵	Bevacizumab Ranibizumab (2) + PDT Ranibizumab (2)	51 M OD 76 M OD	BVMD 20/40 BVMD 20/250	Unknown 20/250	Unknown 108 m	P.Pro297Thr P.Arg218His	
	Khan et al. ³¹	Bevacizumab (1)	9 OD	20/32	20/65	18 m	P.Arg218Cys, ARB	
		Bevacizumab (1)	20 OS	20/40	20/140	18 m	P.Ser16Phe, ARB	
		Bevacizumab (10)	24 OD	20/80	48 m		P.Arg105Gly, ARB	
		Bevacizumab (2)	28 OD	20/32	20/200	24 m	P.Phe298Val, ARB	
		Bevacizumab (1)	18 OD	20/40	20/200	12 m	Not known, ARB	
		Bevacizumab (1)	10 OD	20/32	20/140	10 m	Not known, ARB	
		Bevacizumab (3)	19 OD	20/32	20/200	10 m	Not known, ARB	
	Gliem et al. ⁵³	Aflibercept	15 patients Mean age: 53 (22–65)	20/32	20/32	12 m	SRF present at final follow-up in all eyes. One injection then monthly PRN	
Pseudoxanthoma Elasticum	Iacono et al. ⁷⁰	Bevacizumab	15 patients Mean age: 59 ± 10	20/28	20/50	36 m	Mean #injection = 5.2 ± 2.7 (1–10) at 36 months.	
	Lai et al. ⁹⁴	Ranibizumab Sham	18 patients 9 patients 13 patients 14 eyes	NR NR -3.5 letters 20/50	+11 letters -3.5 letters 20/63	2 m 12 m	Treatment effect of 14.6 letters of ranibizumab compared to sham. Persistence of fluid in 39% after switching.	
	Sekfali et al. ¹⁶⁶	Aflibercept	27 patients 35 eyes	20/43	14% gained 3 lines 49% no change 37% lost 3 lines	49 m (8–66 m)	Mean #injection = 9.9 ± 7.2 (2–26) at 48 months.	
	Tilleul et al. ¹⁸³	Ranibizumab	Mean age: 64 ± 14	20/63	20/50	48 m (36–135)	Persistent angiographic leak in 23%.	
	Torres-Costa et al. ¹⁸⁴	Ranibizumab Bevacizumab Aflibercept	29 patients 39 eyes Mean age: 53 ± 12	20/100	109 m +/- 42 m	Mean #injection = 10.8 ± 9.0 (2–44) at 48 months.		
	Rohart et al. ¹⁶⁰	Ranibizumab Aflibercept Bevacizumab	23 patients 33 eyes Mean age: 57 ± 8			Mean #injection = 21 ± 25 at end of follow-up.		

anti-VEGF = anti-vascular endothelial growth factor; OS = left eye; OD = right eye; PDT = photodynamic therapy; ARB = autosomal recessive bestrophinopathy; MNV = macular neovascularization; BVMD = Best vitelliform macular dystrophy; NR = not reported; PRN = pro re nata.

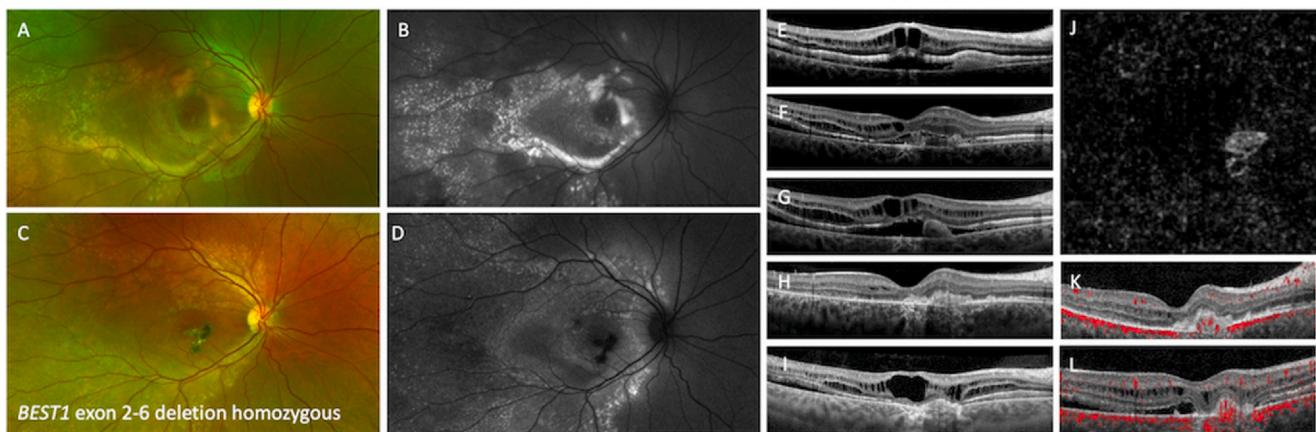


Fig. 5 – Optos imaging of a 9-year-old boy with a genetically confirmed recessive bestrophinopathy showing extensive multifocal subretinal vitelliform lesions (A) that were hyperautofluorescent (B). Visual acuity declined from 6/15–6/19 during 10 years of observation. This was associated with a reduction in the vitelliform lesions and subsequent formation of subfoveal fibrotic scar (C, D). OCT at baseline showed intraretinal cystoid changes with subretinal fluid and vitelliform deposits (E). At age 13, subretinal hyperreflective material was noted adjacent to the fovea (F). A month later, a well-defined PED was noted (G). Six months later, the PED collapsed, accompanied by the resolution of intraretinal and subretinal fluid (H). Intraretinal cystoid changes returned gradually and after 10 years, and there was cystoid cavitation in the macula (I). En face OCT angiography shows a neovascular network (J) that corresponded to the flow signal within the collapsed PED (K). This flow signal persisted with a recurrence of subretinal and intraretinal fluid 2 months later (L).

change significantly over time in 3 patients with type 2 MNV and 1 with type 1 MNV. Type 3 MNV has been reported in recessive bestrophinopathy although the accompanying macular fluid was not responsive to anti-VEGF therapy. This suggests a disrupted blood-retina barrier or RPE pump dysfunction.¹⁹⁶ Indications for treating MNV remain controversial due to our evolving understanding of the life cycle of MNV in relation to the formation of a vitelliform lesion and the presence of SRF. Some advocate for a conservative approach guided by fluorescein leakage,¹⁴¹ while others recommend a trial of anti-VEGF when a transition from stage 2/3 to stage 4 occurs. Here, the intent is to reconstitute SRF and the vitelliform lesion.⁶² Fig. 5 illustrates a case of fluctuating MNV activity in a recessive bestrophinopathy case observed over 10 years without treatment.

3.4. PXE

Angiod streaks in PXE represent breaks in a calcified Bruch membrane, which predisposes to the formation of multifocal MNV in up to 86% of patients^{51,55}. The natural history of untreated MNV in PXE is poor, with visual acuities declining to <20/200 in the fourth decade to the fifth decade due to the development of a disciform scar and atrophy.⁵⁴

A literature review of 54 studies (>160 cases) using anti-VEGF therapy or PDT for PXE-related MNV showed a 6-line improvement in visual acuity with both treatment modalities.⁵⁴ While laser photocoagulation of extrafoveal lesions provided similar results to PDT, the authors cautioned

against its use due to frequent MNV recurrences and laser-induced scotomas.¹⁶⁰ There was no benefit in combining PDT with anti-VEGF therapy.⁵⁴ More recent prospective interventional case series and randomized controlled trials support the safety and efficacy of anti-VEGF monotherapy across all 3 agents (bevacizumab, aflibercept, and ranibizumab),^{53,70,94,142,166} while long-term (>4 years) retrospective case series demonstrated that visual acuity can be maintained with close monitoring and retreatment for MNV recurrences.^{160,166,183,184} A summary of the outcome data from these prospective and retrospective studies is summarized in Table 3. Fig. 6 illustrates a case of PXE with prompt response to 2 anti-VEGF injections with no recurrence after 2 years.

4. Centripetal diseases including choroidal dystrophies

This group of disorders has a predilection for early peripheral retinal involvement with rod greater than cone system dysfunction on electrophysiology. The centripetal IRDs of most interest with respect to MNV are those associated with NR2E3 (MIM#694485) or enhanced S-cone syndrome (ESCS) and CHM (MIM#399389) or choroideremia.

4.1. ESCS or Goldmann-Favre syndrome

Patients with ESCS typically manifest early onset nyctalopia with increased sensitivity to blue light. Visual acuity often remains stable, and electrotoretinography shows a slow

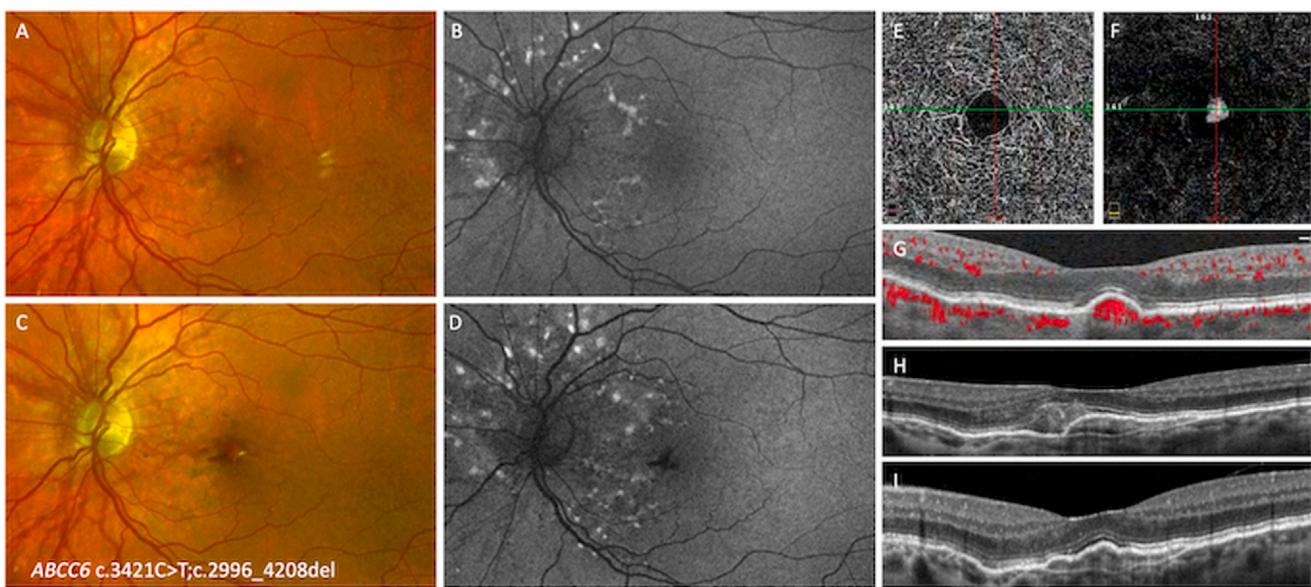


Fig. 6 – Optos imaging of a 46-year-old woman with genetically confirmed pseudoxanthoma elasticum showing angiod streaks (A) and peripapillary hyperautofluorescent subretinal deposits (B). Two years later, she presented with new onset distortion in the left eye due to a subfoveal hemorrhage (C, D). En face OCTA at baseline showed a normal deep vascular plexus (E) and a subfoveal nonexudative vascularized PED as shown by the central flow signal (F) within the PED (G). Two years later, OCT imaging showed subretinal hyperreflective material from the bleed due to active type 1 macular neovascularization. This resolved after receiving 2 ranibizumab injections and visual acuity was maintained at 6/6 at 2 years after treatment.

decline in parallel to age-related changes.³⁰ Color funduscopic examination shows nummular pigmentary changes along the vascular arcades at the level of the RPE in 86%, yellow-white dots in 57%, foveomacular schisis in 41%, torpedo-like lesion in 11%, and circumferential subretinal fibrosis in 7%.³⁰

In a recent large case series, Alsalamah and coworkers⁴ reported subretinal fibrosis in 47% of their cohort and proposed 2 types of stable subretinal fibrotic reactions: a central macular unifocal fibrotic nodule and circumferential subretinal fibrosis. Nowilaty and coworkers hypothesized that the former is closely related to the formation and/or regression of type 3 MNV,^{106,136,195} as demonstrated by FA or OCTA. These 2 phenotypes of subretinal fibrosis do not coexist in the same eye. Retinoochoroidal anastomosis has been observed in children as young as 2 years of age.

Active lesions demonstrating hemorrhage and exudation have been treated with anti-VEGF agents with limited structural and functional improvement. In all cases, the type 3 MNV evolved into a central macular unifocal fibrotic nodule surrounded by a depigmented halo.⁴¹³⁶ One patient in Nowilaty and coworkers' series received a subretinal tissue plasminogen activator for the displacement of a massive subretinal hemorrhage associated with a type 3 MNV resulting in marked visual improvement. These peculiar subretinal fibrotic reactions within the central or paramacular region may lead to a misdiagnosis of inflammatory eye

disease in a pediatric cohort.⁴¹³⁵ Given the recent findings of type 3 MNV in ESCS, further OCTA investigations should be considered when re-examining previously published cases of choroidal neovascularization (i.e., type 1 or type 2 MNV).^{19,27,32,95,114,133,135,162} The role of anti-VEGF therapy in active type 3 MNV remains uncertain. However, a trial of anti-VEGF therapy may have a role in those with acute visual decline secondary to exudative and hemorrhagic type 3 MNV. Fig. 7 illustrates an unusual combination of central and circumferential multifocal subretinal fibrotic lesions in the same eye of a patient with ESCS. The central lesions were type 3 MNV based on OCTA.

4.2. Choroideremia and choroideremia carriers

MNV is a known, but rare, complication seen in choroideremia and CHM carriers. Untreated MNV tends to result in subretinal fibrosis.^{41,148,159,163} Similarly, untreated MNV in CHM carriers results in poor visual outcomes, as shown in 2 previous reports;⁴¹ however, Compos-Pavon and Torres-Pena²⁹ reported spontaneous resolution of MNV in a 30-year-old man with choroideremia, who presented with a visual acuity 20/100 and an associated macular hemorrhage. By 6 months, the MNV had resolved, and vision improved to 20/25.

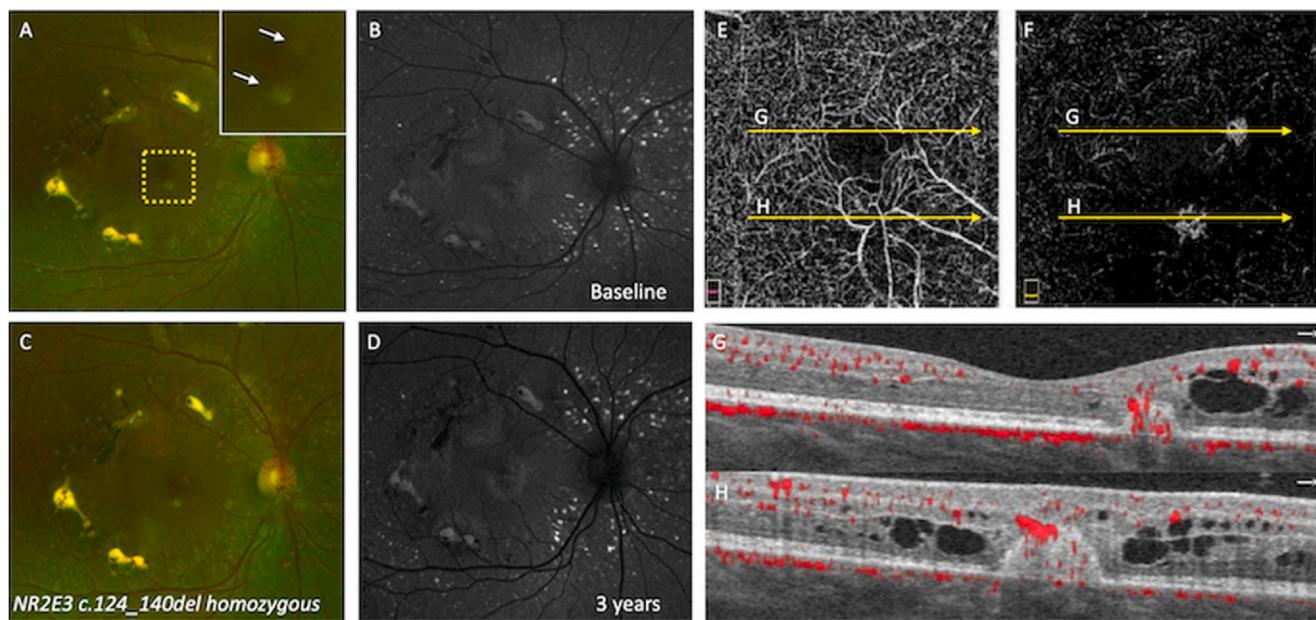


Fig. 7 – Optos imaging (A) of an 18-year-old male with genetically confirmed enhanced S-cone syndrome showing an unusual co-occurrence of central bifocal (2 white arrows in insert) and circumferential multifocal nodular fibrotic lesions. There were peripapillary hyperautofluorescent subretinal deposits (B). Three years later, there was no significant change (C, D). OCT angiography of the deep vascular plexus shows dilated vessels feeding and draining the 2 central nodular fibrotic lesions (E), which had internal flow signals in the outer retina slab (F). Flow signals can be seen connecting the vascular structures within the 2 fibrotic nodules with the retinal vasculature (G, H), indicating a type 3 macular neovascularization (MNV). His visual acuity remained at 6/9.5 in the right eye with no anti-VEGF treatment.

Luttrell and Breazeale¹⁰⁴ reported laser photocoagulation of an extrafoveal MNV in an 11-year-old boy with choroideremia, and vision improved from 20/200 to 20/30. Two reports of bevacizumab in 13-year-old boys with MNV showed that visual acuity could be maintained with 6 and 10 injections, respectively, over a 1-year period.^{34,139} Ranjan and coworkers reported that only 5 ranibizumab injections were required over a 3-year period to treat a 13-year-old male with subfoveal MNV secondary to choroideremia;¹⁵⁶ however, Patel and coworkers¹⁴⁴ reported a case of a 14-year-old boy with choroideremia requiring bevacizumab injections every 4–8 weeks initially in the left eye. Over a period of 16 months, he received a total of 13 injections, and his vision improved from 20/200 to 20/50. At 24 months, no injection was administered, and his vision again dropped to 20/100 with an increase in SRF. OCTA in this case showed a persistent flow signal within the subretinal tissue unlike other reported cases where the MNV lesions resolved completely. Ang and coworkers⁶ described a 44-year-old choroideremia carrier with a subfoveal MNV located at the edge of myopic chorioretinal atrophy. Macular fluid responded promptly to anti-VEGF injections, but recurrences over 2 years and 10 months required a total of 14 injections. Given the severe myopic chorioretinal atrophy and the location of the new vessel, it may be more

likely that the MNV was secondary to myopia. Fig. 8 illustrates a case of a female CHM carrier with type 2 MNV responding promptly to anti-VEGF treatment with no recurrence following 2 years of observation.

4.3. Other choroidal dystrophies and RP

Three choroidal dystrophies have been associated with MNV: GA (MIM#258870), Bietti crystalline corneoretinal dystrophy (MIM#210370), and dominant RPE65-related chorioretinal dystrophy (RP87, MIM#618697). Furthermore, 10 cases of genetically uncharacterized RP have reported MNV.

GA, caused by a deficiency in the vitamin B6-dependent mitochondrial matrix enzyme ornithine ketoacid aminotransferase, has been associated with subfoveal MNV.¹¹² Chatziralli and coworkers³³ reported a 35-year-old male with GA responding promptly to 3 ranibizumab injections with no recurrence of SRF at 6 months. His visual acuity improved from 6/60 to 6/48. Inanc and coworkers⁷¹ reported a 20-year-old man with bilateral MNV responding to a single dose of bevacizumab with no additional treatment required at 1 year.

Bietti crystalline corneoretinal dystrophy is caused by biallelic mutations in CYP4V2 and results in altered fatty acid metabolism. Bietti crystalline corneoretinal dystrophy has

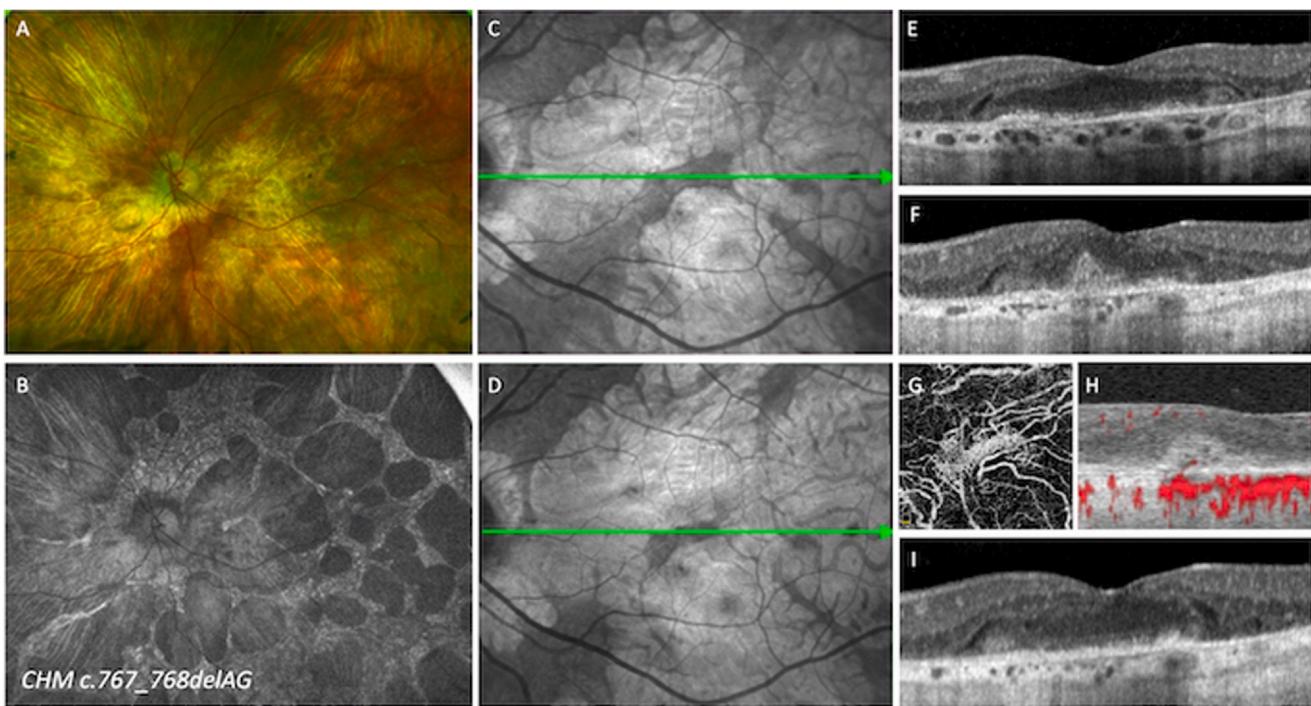


Fig. 8 – Optos imaging of a 58-year-old female choroideremia carrier showing diffuse chorioretinal atrophy (A) and large well-defined regions of RPE atrophy throughout the fundus (B). Near-infrared reflectance at baseline showed a central island of RPE remaining supporting a visual acuity of 6/7.5 (C). This small island reduced in size over 4 years (D) when she returned with a sudden reduction in vision to 6/15. OCT at baseline showed central preservation of the outer nuclear layers in the fovea (E). A subfoveal hyperreflective lesion developed 4 years later coinciding with acute vision loss (F). OCT angiography showed loss of the choriocapillaris outside the central RPE island (G) and a small speck of flow signal within the type 2 macular neovascularization. This hyperreflective lesion resolved after 2 ranibizumab injections, and visual acuity was maintained at 6/12 without further injections for another 2 years.

been associated with peripapillary choroidal neovascularization⁸ and MNV.^{46,61,90,101,108,111,130,182,188} Several cases reported the presence of subretinal fibrosis at presentation suggestive of a self-limiting natural history.^{61,90} Other case reports demonstrated regression of MNV to a fibrotic scar with anti-VEGF therapy.^{46,108,130,182} Given the similar anatomical outcomes, it remains to be seen if anti-VEGF therapy is superior to observation.

Dominant RPE65-related chorioretinal dystrophy has been shown to develop MNV in 1 member of an Australian family harboring the RPE65 p.(Asp477Gly) variant.¹⁴⁰ The coinheritance of a BEST1 p.(Arg13Cys) may have contributed to the formation of this stable MNV lesion over 4 years of observation. To date, only 10 cases of ungenotyped RP have been reported to develop MNV. Seven^{13,35,73,107,111} had type 2 MNV, and 3 had type 3 MNV.^{2132,164} These cases were treated with laser photocoagulation,¹¹¹ PDT,³⁵ or anti-VEGF agents^{2,13,107,164} with variable visual outcomes. Type 2 MNV secondary to RP required between 1 and 5 injections during the first year,^{13,107} while type 3 MNV required 8–10 injections.³¹⁶⁴ As previously discussed, MNV secondary to PRPH2-

related RP may require more intensive and ongoing use of anti-VEGF agents.^{125,137} Fig. 9 illustrates a case of dominant RP and an x-linked RP carrier with untreated MNV.

4.4. Iatrogenic MNV secondary to gene therapy

Advancements in subretinal gene therapy hold promise for the stabilization and even reversal of some IRDs. Recent progress in clinical trials and regulatory approval of subretinal voretigene neparvovec gene therapy (Luxturna™) for RPE65-associated retinopathy requires clinicians to be aware of any potential complications following these surgical procedures. Traumatic MNV has been reported with vitreoretinal surgery. Price and coworkers¹⁵⁰ documented a case of iatrogenic MNV developing 1 month post Luxturna™ surgery. Intraoperatively, a small subretinal hemorrhage was noted beneath the retinotomy site. Postoperatively, multimodal imaging was able to identify a break in Bruch membrane at the retinotomy site outside the macula region. Notably, the 16-year-old remained asymptomatic and the MNV regressed spontaneously without treatment.

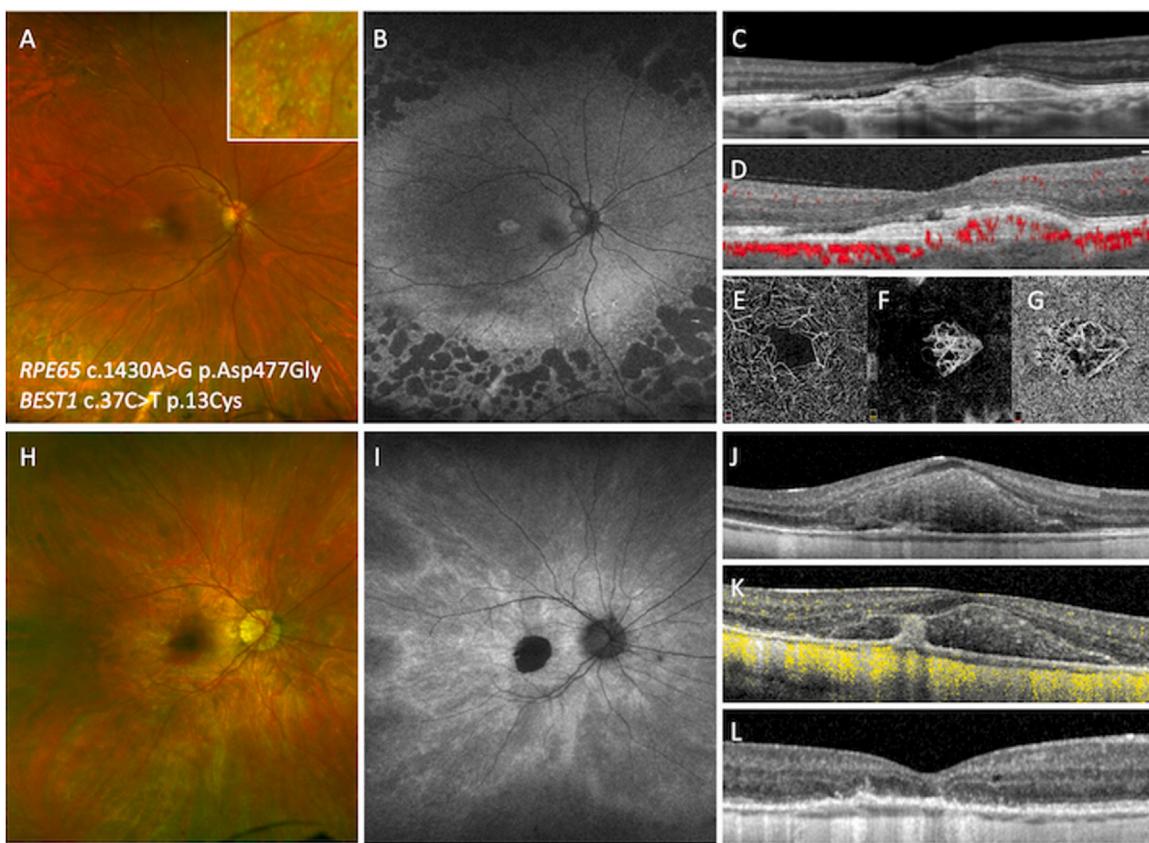


Fig. 9 – Optos imaging of a 63-year-old male with genetically confirmed dominant retinitis pigmentosa characterized by bone spicules and white dots peripherally (A). Areas of hypoautofluorescent were seen in the mid-peripheral retina (B). OCT at baseline showed a PED with shallow subretinal fluid (C). Given the absence of recent visual decline, this was observed for 4 years with stable visual acuity of 6/9.5. At the most recent visit, OCT angiography confirmed a stable type 1 macular neovascularization (MNV) (D) with normal deep retinal vascular plexus (E), a neovascular network within the outer retinal layer (F), and preserved choriocapillaris surrounding the type 1 MNV. Optos imaging of a 21-year-old female carrier with a history of x-linked retinitis pigmentosa showing subfoveal hemorrhage (H) and the typical tapetal-like reflex on fundus autofluorescence imaging (I). OCT at baseline showed thick subfoveal hyperreflective blood reducing visual acuity to 6/30. Angiography did not show leakage, and the patient returned 2 weeks later with OCT angiography showing a reduction in the submacular hemorrhage with no convincing flow signal within the nodular lesion arising from the RPE layer (K). After 7 months of observation, the subretinal hemorrhage had resolved spontaneously but visual acuity only returned to 6/15 (compared to 6/9.5 prior to the bleed) due to disruption of the outer retinal layers.

5. Conclusions

This review highlights the diverse phenotypic spectrum of IRD-related MNV and the clinical utility of multimodal imaging including OCTA for the accurate diagnosis and monitoring of treatment responses and documenting the natural history. To date, OCTA has enabled the detection, characterization, and quantification of CNV size and facilitated an assessment of treatment responses in patients with IRDs despite their often distorted intraretinal and subretinal architecture. Although the literature contains reports of spontaneous MNV regression, most have demonstrated the resolution of intraretinal fluid and SRF in response to intravitreal anti-VEGF treatment. Given the rarity of many IRDs, international collaboration is required to harness adequate sample sizes for randomized controlled trials examining

structural and functional outcomes using well-defined treatment protocols. Importantly, clinicians caring for IRD patients should consider the possibility of MNV development when patients present with acute visual loss and offer timely treatment with anti-VEGF to prevent irreversible changes.

5.1. Methods of literature search

We conducted a systemic Medline database search on PubMed (October 10, 2022) using the following MeSH headings: choroidal neovascularization, MNV, RP, retinal dystrophy, macular dystrophy, Stargardt disease, pattern dystrophy, vitelliform macular dystrophy, choroidal dystrophy, ABCA4-associated retinal dystrophy, SFD, LORD, DHRD, PXE, angioid streaks, BEST1, NR2E3, ESCS, autosomal recessive bestrophinopathy, peripherinopathy, ABCC6, choroideremia, GA, pattern dystrophy, PRPH2-associated

retinal dystrophy, RPE65-related chorioretinal dystrophy, CYP4V2, OCTA, and anti-VEGF to identify publications through June 11, 2023 (no lower time limit imposed). We identified further articles from the reference lists of the retrieved articles. This review primarily relied on articles written in English. However, we reviewed non-English language articles that had abstracts translated.

Disclosures

The authors report no commercial or proprietary interest in any product or concept discussed in this article.

Ethics statement

Patients have given consent for these images to be used in a prospective study approved by the Human Research Ethics Office of the University of Western Australia (2021/ET000151).

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Declaration of Competing Interest

None.

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