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INHERITED RETINAL DISEASE GENE PANEL IN POSTERIOR OR PANUVEITIS WITH DYSTROPHIC FEATURES

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Purpose: To evaluate the presence of American College of Medical Genetics and Genomics class 3, 4, and 5 genetic variants in inherited retinal disease (IRD) genes in posterior or panuveitis with dystrophic features (PUD) in a Belgian cohort.

Methods: Multicentric, retrospective study of PUD cases diagnosed between January 2012 and February 2022. Inherited retinal disease gene panels were analyzed in every patient. Three PUD categories were defined as follows: idiopathic posterior or panuveitis with retinitis pigmentosa-like features (PURPL), idiopathic posterior or panuveitis with other dystrophic features (PUOD), and posterior or panuveitis with established ophthalmological or systemic etiology and dystrophic features (POSED).

Results: The authors included 12 patients (7 women, 5 men). The mean age at inclusion was 52.2 years (26–80 years). Three patients demonstrated class 4 or 5 variants in genes that led to a diagnostic reclassification. One patient had a class 3 variant in an X-linked IRD gene that possibly explained his phenotype. Seven patients had variants in IRD genes that could not explain their phenotype. One patient had a negative panel result.

Conclusion: Inherited retinal disease gene panel analysis allowed diagnosis refinement in 3/12 (25%) patients in the PUD cohort, all belonging to the PURPL subgroup. The authors recommend that all patients with PURPL benefit from gene panel testing to avoid overlooking undiagnosed IRDs.

RETINA 45:509–521, 2025

Ocular inflammatory features such as anterior chamber (AC) cells, vitreous cells, and intraretinal cystic spaces with vascular leakage on fluorescein angiogram (FA) can be seen in progressive inherited retinal diseases (IRD). Specifically, they are primarily found in cases of retinitis pigmentosa (RP).[1–5]

The prevalence of intraocular inflammatory findings in the context of IRD has been reported to vary from 0.26% to 37.3%, depending on the methodology used for counting cells, the site of inflammation, and the IRD subgroup studied.[1,2,6] The inflammation is generally localized to either the vitreous cavity or the retinal vessels and capillaries, but it can also affect both simultaneously.[2–4,6] AC inflammation is less frequently reported, although it has been described in the context of RP.[1] Intraocular levels of various proinflammatory cytokines and chemokines, such as IL-8, MCP-1, and IL-6, have been shown to be elevated in aqueous and vitreous samples in cases of RP.[6]

Some genes are known to be associated with inflammatory IRD presentations, most prominently *CRB1*.[3,5,7] Moreover, certain syndromic disorders can be associated with inflammatory retinal dystrophies, i.e., ROSAH (retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache) syndrome, which is due to heterozygous pathogenic variants in *ALPK1*, and CBL syndrome, which is caused by heterozygous pathogenic variants in *CBL*.[8–10]

In addition, certain retinal dystrophies have notoriously been described as pseudo-inflammatory, like Sorsby fundus dystrophy, and it has recently been proposed that this entity could benefit from anti-inflammatory therapy with intravitreal corticosteroids or TNFα antagonists, to control macular choroidal neovascularization.[11,12] On top of that, certain chronic uveitis cases can evolve toward a phenotype with retinal pigmentary changes that ultimately mimic RP.[13]

With this information in mind, it is reasonable to assume that misdiagnosis of inflammatory IRD as

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uveitis may be a relatively common occurrence. Two studies looking at uveitis masquerade syndromes identified hereditary ocular disorders that could explain the intraocular inflammation in 12.5% to 31% of patients.[14,15] Another study reported 6 IRD cases initially misdiagnosed as intermediate uveitis with severe cystoid macular edema (CME). It is noteworthy that 3/6 (50%) patients in this cohort were in fact *CRB1*-related IRD.[3]

In short, distinguishing between an inflammatory IRD and an idiopathic uveitis can be rather challenging, especially when the inflammatory features are exaggerated or severe. We set out to analyze these cases with IRD gene panels to determine if there were undiagnosed IRDs in our cohort of patients with posterior or panuveitis and dystrophic features (PUD).

Methods

Ethics Committee

The research adhered to the tenets set forth in the Declaration of Helsinki and was approved by the ethics committee of Saint-Pierre University Hospital (CE/22-04-06), which served as the central committee for all centers.

Study design

We performed a multicentric retrospective study on patients diagnosed with PUD between January 2012 and February 2022 within two academic Ophthalmology departments (Saint-Pierre University Hospital and Brugmann University Hospital) and one Center for Medical Genetics (Ghent University Hospital) in Belgium.

Definitions

Posterior uveitis was defined according to the Standardization of Uveitis Nomenclature guidelines as primary retinal or choroidal inflammation, including retinal vasculitis.[16] Panuveitis was likewise defined according to Standardization of Uveitis Nomenclature guidelines as simultaneous inflammation of the anterior segment, the vitreous, and the retina or the choroid, with no predominant site of inflammation.[16]

Retinitis pigmentosa-like (RPL) dystrophic features were defined as features reminiscent of classic RP, e.g., peripheral intraretinal pigment clumping, midperipheral retinal atrophy, perifoveal or perimacular hyperautofluorescent rings on blue light autofluorescence (BAF), and perifoveal outer retinal atrophy (ORA) on macular spectral-domain optical coherence tomography (SD-OCT).

Other dystrophic features (ODF) were defined as any abnormal dystrophic retinal feature distinct from the ones mentioned above. These include BAF changes unusual for RP, vascular changes, or fibrotic changes. Consideration as to what represented dystrophic changes as opposed to degenerative changes, or any other changes due to another cause of retinal pathology, was left to the discretion of the treating physician.

Uveitis Work-up

All patients had a uveitis work-up consisting of at a minimum syphilis serology (nontreponemal and treponemal test), interferon-gamma release assay or tuberculin skin test, angiotensin converting enzyme, and computed tomography scan of the chest. Additional tests such as Lyme serology or class I HLA typing were ordered on a case-by-case basis, whenever deemed necessary by the treating physician.

Patients and Clinical Data Collection

A cohort of 12 patients fitting these criteria was analyzed. A complete general and ophthalmological history was obtained from all patients. A potential family history of hereditary ocular disorders was specifically evaluated. Complete ophthalmological examination results were recorded, including best-corrected visual acuity, intraocular pressure, slit-lamp examination, and fundoscopy. Parameters of intraocular inflammation such as AC cells or vitreous cells were recorded according to Standardization of Uveitis Nomenclature guidelines.[16] Reviewed ancillary testing

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Funding for the study was granted from the Association Vésale in Brussels, grant reference number FDCD/079/22/cc.

The following authors have no proprietary interests or financial disclosures (e.g., consultancies, stock ownership, equity interest, and patent/licensing arrangements): S. Abramowicz, A. Meunier, D. Draganova, L. Caspers, M. De Bruyne, S. Van de Sompele, E. De Baere, B. P. Leroy, L. Postelmans. F. Willermain has been part of advisory board for AbbVie and Horus Pharma.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

The study was performed at the Departments of Ophthalmology of Saint-Pierre University Hospital and Brugmann University Hospital, and the Center for Medical Genetics of Ghent University Hospital.

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included macular SD-OCT, BAF, FA, indocyanine green angiography, either Humphrey visual fields (VFs) or Goldmann VFs based on availability of data, and full-field electroretinogram (ERG). Electroretinograms were recorded according to International Society for Clinical Electrophysiology of Vision standards.[17] Spectral-domain optical coherence tomography, BAF, and FA were captured using Spectralis (Heidelberg Engineering, Germany). Color fundus photography was obtained using either the Cobra (CSO, Firenze Italy) or the Zeiss Visucam Pro NM (Carl Zeiss Meditec AG, Jena, Germany) fundus cameras.

Genetic Analysis

Whole-exome sequencing-based IRD gene panel analysis was performed in every patient. Analyses were performed between 2018 and 2022. Genomic DNA was enriched with the SureSelectXT Low Input Human All Exon V7 (Agilent Technologies, Inc.), followed by sequencing on a HiSeq 3000 platform (Illumina) (2018–2019) or NovaSeq 6000 platform (Illumina) (2019–2022). Data analysis was executed as described in the internal protocol of the Center for Medical Genetics of Ghent University Hospital and was limited to genes present in version 4 (2018–2020) or 5 (2020–2022) of the RetNet gene panel (https://www.cmgg.be/assets/bestanden/Genpanel-RETNET-v4.pdf; https://www.cmgg.be/assets/bestanden/Genpanel-RETNET-v5.pdf), respectively containing 276 and 290 IRD genes. At least 90% of investigated genes had a coverage of 20× or more. Variants with a low-quality score were confirmed with an independent analysis using Sanger sequencing. Results were technically validated by a clinical laboratory expert and medically validated by a clinical geneticist. Variants were classified across the five categories of pathogenicity established by the American College of Medical Genetics[18] using an in-house developed tool based on the American College of Medical Genetics and Association for Clinical Genomic Science guidelines (www.acgs.uk.com/quality/best-practice-guidelines/). The five categories are: benign (class 1), likely benign (class 2), variant of unknown significance (VUS, class 3), likely pathogenic (class 4), and pathogenic (class 5). Compatibility of genotypes and phenotypes was evaluated by a multidisciplinary team of clinical geneticists, ophthalmologists, and clinical laboratory experts specialized in ophthalmic genetics.

Panuveitis With Dystrophic Features Category Determination

We established three PUD categories: idiopathic posterior or panuveitis with RP-like features (PURPL), idiopathic posterior or panuveitis with other dystrophic features (PUOD), and posterior or panuveitis with established ophthalmological or systemic etiology and dystrophic features (POSED).

The PURPL subgroup was defined as posterior or panuveitides with a negative uveitis work-up and RPL dystrophic features. PUOD was defined as posterior or panuveitides with a negative work-up and ODF. Finally, POSED was defined as posterior or panuveitides in which an established ophthalmological (multifocal choroiditis, Birdshot retinochoroiditis, etc.), systemic (sarcoidosis, Behçet's disease, etc.), or infectious (syphilis, tuberculosis, Lyme disease, etc.) cause was diagnosed, and where either RPL or ODF was found.

Figure 1 shows examples of PURPL (A–L), PUOD (M–R), and POSED (S–Z*) patients.

Results

General Patient Characteristics and Main Results of Ophthalmological Examination

A cohort of 12 patients (7 women, 5 men) was included. The mean age at inclusion was 52.2 years (26–80 years). None of the patients had a history of hereditary ocular disorders. The most frequent main complaint was subjective decreased best-corrected visual acuity, which was present in 7/12 (58%) patients. Nyctalopia was the second most frequent complaint, mentioned by 4/12 (33%) patients. Outer retinal atrophy on macular SD-OCT was present in 10/12 (83%) patients. Hyperautofluorescent rings were seen bilaterally in 4/12 (33%) patients and unilaterally in 1/12 (8%) patients. ERGs demonstrated more extensive rod than cone dysfunction in a bilateral and symmetrical fashion in 7/12 (58%) patients, whereas unilateral rod-cone dysfunction was noted in 2/12 (17%) patients. Table 1 shows complete patient characteristics and results of the ophthalmological examination.

Uveitis Characteristics, Work-up, Treatment, and PUD Category

Table 2 shows detailed results of uveitis characteristics, work-up, treatment, and PUD category. Anterior involvement in the form of granulomatous keratic precipitates and AC cells was found in 3/12 (25%) patients, none with more than 1+ cells. Vitreous cells were observed in 7/12 (58%) patients, never exceeding 2+ cells. Posterior involvement in the form of vascular leakage was observed in 9/12 (75%) patients, with an origin from capillaries in 8/9 (89%), disc vessels in 5/9 (56%), veins in 3/9 (33%), and arteries in 1/9 (11%) patients. Intraretinal cystic spaces were present in 5/12 (42%) patients.

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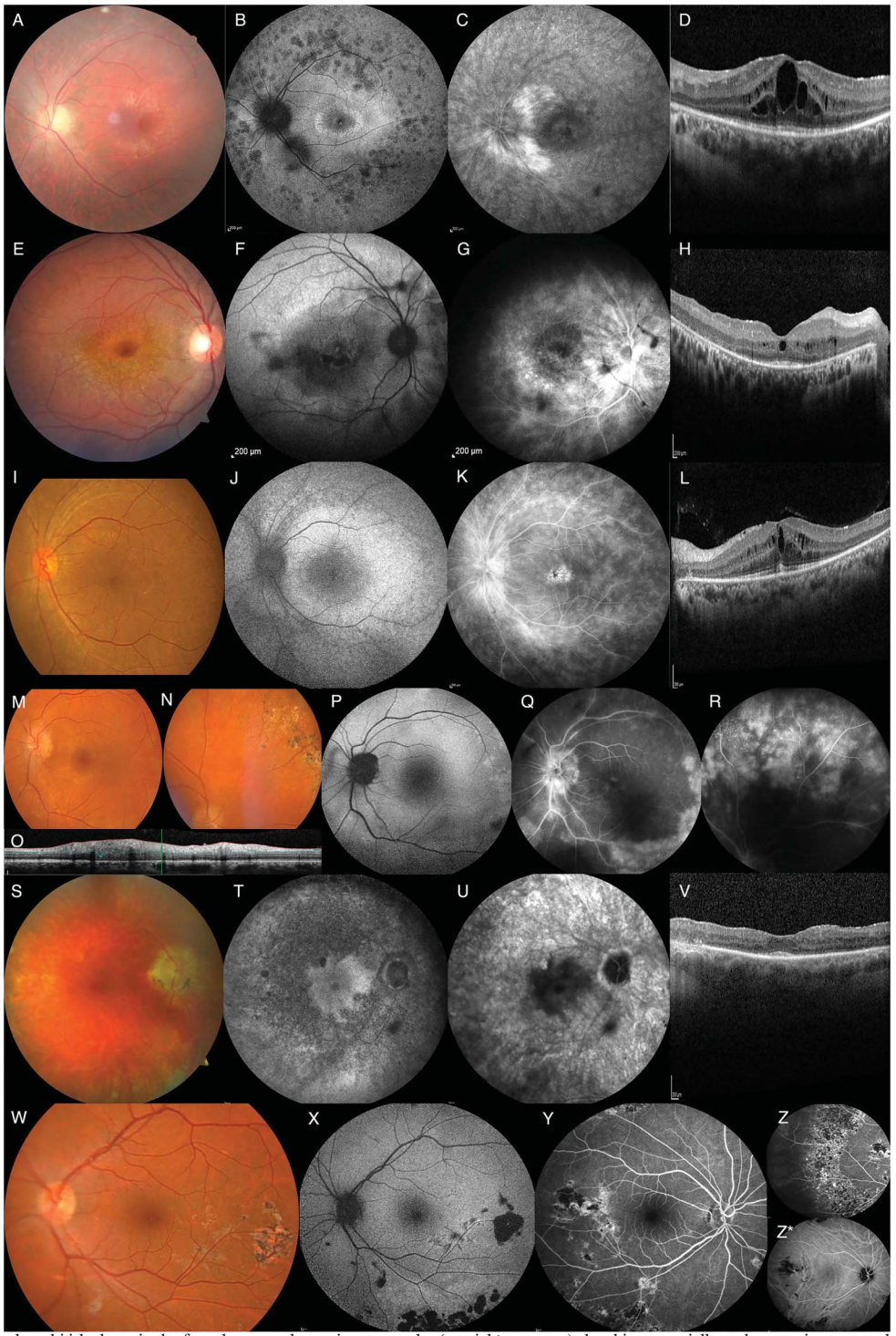

Fig. 1. Multimodal imaging of cases 1, 3, 4, 7, 9, and 10. **A–D**. Case 1—*EYS*-related autosomal recessive retinitis pigmentosa, left eye: **A**, fundoscopy showing mild temporal disc pallor, cellophane maculopathy, vascular attenuation, and subtle midperipheral ORA. **B.** Blue light autofluorescence showing a perifoveal hyperautofluorescent ring and patchy midperipheral hypoautofluorescence. **C.** Fluorescein angiogram showing generalized hyperfluorescence of the posterior pole extending beyond the vascular arcades, and marked peripapillary capillary leakage as well as petaloid leakage at the fovea. **D.** Macular SD-OCT, showing marked intraretinal cystic changes at the level of the inner nuclear layer and outer nuclear layer, and symmetrical perifoveal ORA. **E–H.** Case 3—*CRB1*-related ARRP, right eye: **E**, fundoscopy showing zones of pigment mottling and hypopigmentation at the level of the macula. **F.** Blue light autofluorescence showing a central heterogeneous zone and a mild perimacular hyperautofluorescent ring. **G.** Fluorescein angiogram showing a central annular hyperfluorescent zone and multifocal leakage (optic disc, fovea, capillaries). **H.** Macular SD-OCT showing perifoveal ORA, thickened aspect of the macula, irregular retinal lamination, and cystic changes in the inner nuclear layer. **I—L**. Case 4—idiopathic posterior or panuveitis with RP-like features, left eye: **I**, fundoscopy showing subtle midperipheral ORA and mild vascular attenuation. **J.** Blue light autofluorescence showing a perimacular hyperautofluorescent ring and subtle patchy midperipheral hypoautofluorescence. **K.** Fluorescein angiogram showing severe multifocal leakage (optic disc, fovea, capillaries, veins). **L.** Macular SD-OCT, showing perifoveal ORA, and intraretinal cystic changes at the level of the inner nuclear layer and outer nuclear layer. **M–R.** Case 7—idiopathic posterior or panuveitis with other dystrophic features (PUOD): **M**, fundoscopy of the left eye showing optic nerve edema, a mild annular whitish sheen in the foveal area, and prominent vascular (arterial > venous) sheathing especially at the superior temporal arcade. **N.** Fundoscopy of the right eye showing optic nerve edema, prominent arterio-venous sheathing, and peripheral zones of fibrotic and pigmentary changes arranged in a honeycomb pattern. **O.** Optic nerve SD-OCT of the right eye, showing prominent edema of the retinal nerve fiber layer. **P.** Blue light autofluorescence of the left eye, showing patchy hyperautofluorescent changes in the temporal macula. **Q.** Fluorescein angiogram of the left eye, showing severe multifocal leakage (optic disc, veins, arteries, capillaries). **R.** Midperipheral fluorescein angiogram of the left eye showing severe leakage (capillaries, veins). **S–V.** Case 9—possible *RP2*-related X-linked RP initially diagnosed as late-stage birdshot retinochoroiditis, right eye: **S**, fundoscopy showing a pale optic disc, peripapillary atrophy, generalized atrophic appearance of the retina with a hypopigmented fundus, and marked vascular attenuation. **T.** BAF showing generalized hypoautofluorescence with foveal sparing. **U.** Fluorescein angiogram showing generalized window defects over the posterior pole with rare hypofluorescent spots in the nasal periphery. **V.** Macular SD-OCT showing severe perifoveal ORA and an epiretinal membrane. **W—Z*.** Case 10—multifocal choroiditis: **W**, fundoscopy of the left eye showing multifocal chorioretinal scars (CRS). **X.** Blue light autofluorescence of the left eye, showing multifocal hypoautofluorescent spots at the level of the CRS, along with some subtle surrounding hyperautofluorescence. **Y.** Fluorescein angiogram of the right eye showing heterogeneous hyperfluorescence and hypofluorescence at the level of the CRS. **Z.** Midperipheral fluorescein angiogram of the right eye showing the same pattern of fluorescence as in the posterior pole. Note the concentric disposition of the midperipheral lesions. **Z*.** Indocyanine green angiography of the right eye showing hypofluorescence at the level of the CRS FA, fluorescein angiogram.

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Table 1. General Patient Characteristics and Main Results of Ophthalmological Examination

Pt	Age at Onset, at Inclusion	Sex	Ethnicity	Laterality, Symptoms	BCVA at Presentation	Main Pathological Fundus Changes and Abnormal Ancillary Examination results*
1	18, 26	M	Moroccan	B/L, ↓ BCVA, nyctalopia	20/32; 20/25	Fundus: ORA, ERM, VAt. Macular SD-OCT: Perifoveal ORA BAF: Foveal hyperAF ring, patchy midperipheral hypoAF. ffERG: RCD
2	52, 68	F	Moroccan	B/L, ↓ BCVA, nyctalopia	20/100; 20/200	Fundus: ORA, rare peripheral PM, severe VAt, macular fibrovascular scar OS. Macular SD-OCT: Perifoveal ORA, CME, foveal SRNVM OS. BAF: Patchy midperipheral hypoAF, heterogeneous zone centrally OS. ffERG: RCD
3	20, 28	M	Moroccan	B/L, ↓ BCVA, nyctalopia, VF constriction	20/32; 20/32	Fundus: ORA, macular pigment mottling. Macular SD-OCT: Perifoveal ORA, thickened aspect of the retina, irregular retinal lamination, CME. BAF: Central heterogeneous annular hypoAF zone, perimacular hyperAF ring, periarteriolar hyperAF. ffERG: RCD
4	61, 63	F	Chinese	B/L, ↓ BCVA, nyctalopia	20/50; 20/32	Fundus: ORA, rare peripheral PM, mild VAt. Macular SD-OCT: Perifoveal ORA, CME, ERM BAF: perimacular hyperAF ring, patchy midperipheral hypoAF. ffERG: RCD
5	38, 39	F	Guinean	B/L, none	20/20; 20/20	Fundus: ORA, rare peripheral PM. Macular SD-OCT: perifoveal ORA. BAF: Foveal hyperAF ring. ffERG: Normal
6	43, 56	F	Rwandan	B/L, ↓ BCVA, pain	20/20; CF	Fundus: VAt with generalized whitish vascular sheathing, macular hole OS Macular SD-OCT: OD: normal. OS: macular hole. BAF: not available. ffERG: RCD
7	54, 61	F	Belgian	B/L, none	20/40; 20/100	Fundus: optic nerve edema, peripheral zones of fibrotic and pigmentary changes in a honeycomb pattern, arterio-venous sheathing. Macular SD-OCT: normal. BAF: patchy hyperAF changes in the temporal macula. ffERG: Reduced b:a ratio on single-flash photopic ERG

(*continued on next page*)

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Table 1. (*Continued*)

Pt	Age at Onset, at Inclusion	Sex	Ethnicity	Laterality, Symptoms	BCVA at Presentation	Main Pathological Fundus Changes and Abnormal Ancillary Examination results*
8	45, 51	M	Moroccan	U/L OS, photophobia, redness, pain	20/20; 20/25	Fundus: OS: hyperemic swollen optic disc, and CR edema early in evolution, later appearance of a peripapillary greyish hue and a reddish discoloration of the posterior pole. Macular SD-OCT: OS: foveal SRD, optic nerve edema with peripapillary SRD, retinal folds, and CR edema early in the evolution, later appearance of perifoveal ORA with CME. BAF: OS: geographic hyperAF changes. ffERG: OS: RCD
9	68, 80	M	Belgian	B/L, VF defects	HM; HM	Fundus: Optic disc pallor, peripapillary atrophy, generalized ORA with hypopigmented fundus, marked VAt Macular SD-OCT: severe ORA. BAF: Generalized hypoAF with foveal sparing. ffERG: RCD
10	54, 54	F	Greek	B/L, photopsia	20/20; 20/20	Fundus: Temporal macular and midperipheral concentric nummular CR scarring with PM Macular SD-OCT: ORA at the level of CR scars. BAF: HypoAF at the level of the CR scars. ffERG: normal
11	31, 48	F	Moroccan	B/L, ↓ BCVA	20/25; 20/25	Fundus: multifocal CR lesions, inferior candle-wax drippings OD. Macular SD-OCT: Perifoveal ORA BAF: OD: peripapillary hyperAF changes. OS: foveal hyperAF ring. ffERG: RCD
12	28, 53	M	Belgian	U/L OD, ↓ BCVA	20/25; S/p enucleation	Fundus: OD: Pale optic disc, ERM, Dalen-Fuchs nodules, inferior retinoschisis early in evolution, after Vx for schisis: Abundant spicular PM and VAt inferiorly. Macular SD-OCT: OD: perifoveal ORA, ERM BAF: OD: large hypoAF zone at level of the fovea and the inferior macula. ffERG: OD: RCD

*Results are considered symmetrical for both eyes, except where otherwise specified.

↓, decreased; BAF, blue light autofluorescence; BCVA, best-corrected visual acuity; B/L, bilateral; CF, count fingers; CME, cystoid macular edema; CR, chorioretinal; ERM, epiretinal membrane; F, female; FA, fluorescein angiogram; ffERG, full-field electroretinogram; HM, hand motion; hyperAF, hyperautofluorescence; hypoAF, hypoautofluorescence; M, male; ORA, outer retinal atrophy; PM, pigment migration; Pt., patient; RCD, rod-cone dysfunction; S/p, status post; SRD, serous retinal detachment; SRNVM, subretinal neovascular membrane; U/L, unilateral; VAt, vascular attenuation; Vx, vitrectomy.

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Table 2. Uveitis Characteristics, Work-up, Treatment, and Posterior or Panuveitis With Dystrophic Features Category

Pt	KPs, AC Cells, Synechiae	Vitreous Cells	Vascular Leakage	ICS	ON Edema	Choroidal Involvement	Other	WU	Uveitis Subtype	Treatment	PUD Category
1	—*	—	Capillaries (pp)	+	—	—	—	—	iPU	BEV IVT, DEX IVT, MTX IVT, MPS, MTX, IFX, TCZ	PURPL
2	—	—	Capillaries (pe)	+	—	—	SRNVM OS	↑ ACE	iPU	BEV IVT, MPS, MTX, IFX	PURPL
3	—	1+, snowballs	Capillaries (pp & pe), optic disc	+	+	—	—	—	iPU	—	PURPL
4	—	—	Veins, capillaries (pp & pe), optic disc	+	—	—	ERM OS	—	iPU	DEX IVT, MPS, MTX, ADA, TCZ	PURPL
5	—	0.5+	Capillaries (pp)	—	—	—	Foveal crystals	IGRA +, HLA-B51	iPU	—	PURPL
6	—	1+	Capillaries (pp & pe), optic disc	—	—	—	MH OS	—	iPU	Vitrectomy with silicone oil OS	PURPL
7	—	—	Veins, arteries, capillaries (pp & pe), optic disc	—	+	—	Peripheral fibrosis	—	iPU	—	PUOD
8	G+ KPs, 1+ AC cells	2+	Veins, optic disc	+	+	Stromal choroiditis	SRD, PS	—	iPanU	MPS, MTX, CsA	PUOD
9	—	OD: 1+ OS: 0.5+	—	—	—	—	—	HLA-A29	Late-stage BRC	—	POSED
10	—	—	—	—	—	Multifocal CR atrophic lesions	—	↑ ACE	MFC	—	POSED
11	G+ KPs, 1+ AC cells, posterior synechiae	2+	Capillaries (pp & pe)	—	—	Multifocal choroidal nodules	—	↑ lysozyme, IGRA -	Sarcoid panuveitis	DEX IVT, MPS, MTX, ADA	POSED
12	G+ KPs, 1+ AC cells	1+	—	—	—	Dalen-Fuchs nodules	—	—	SO	MPS, MTX, MMF, AZA, CsA, CB, IFX, TCZ	POSED

Results are considered symmetrical for both eyes, except where otherwise specified. All cases are bilateral except Case 8, which was unilateral in OS, and case 12, which was unilateral in OD.

*All uveitis parameters are reported according to Standardization of Uveitis Nomenclature guidelines. A dash indicates normal findings or negative results.

↑, elevated; AC, anterior chamber; ACE, angiotensin converting enzyme; ADA, adalimumab; AZA, azathioprine; BRC, birdshot retinochoroiditis; BEV, bevacizumab; CB, chlorambucil; CR, chorioretinal; CsA, cyclosporin A; DEX, dexamethasone implant; ERM, epiretinal membrane; G+, granulomatous; ICS, intraretinal cystic spaces; IFX, infliximab; IGRA, interferon-gamma release assay; iPanU, idiopathic panuveitis; iPU, idiopathic posterior uveitis; IVT, intravitreal therapy; KPs, keratic precipitates; MFC, multifocal choroiditis; MH, macular hole; MMF, mycophenolate mofetil; MPS, methylprednisolone; MTX, methotrexate; ON, optic nerve; pe, peripheral; POSED, posterior or panuveitis with established ophthalmological or systemic etiology and dystrophic features; pp, posterior pole; PS; posterior scleritis; Pt, patient; PUD, posterior or panuveitis and dystrophic features; PUOD, idiopathic posterior or panuveitis with other dystrophic features; PURPL, idiopathic posterior or panuveitis with RP-like features; SO, sympathetic ophthalmia; SRD, serous retinal detachment; SRNVM, subretinal neovascular membrane; TCZ, tocilizumab; WU, work-up.

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Evaluation of the clinical presentation in combination with a targeted work-up allowed us to establish a specific ophthalmological or systemic diagnosis in four (33%) patients. Seven (58%) patients were diagnosed with idiopathic posterior uveitis with a main inflammatory involvement in the form of retinal vasculitis or capillaritis. One (8%) patient was diagnosed with a unilateral idiopathic granulomatous panuveitis.

Systemic treatment was proposed in 6/12 (50%) patients and comprised intravenous and oral corticosteroids, conventional disease-modifying antirheumatic drugs (cDMARDs), and biologic DMARDs (bDMARDs). Intravitreal treatment was offered to 4/12 (33%) patients, i.e., antivascular endothelial growth factor (anti-VEGF, bevacizumab) in patients 1 and 2, intravitreal dexamethasone implant (DEX implant, Ozurdex, Allergan Inc, Irvine, CA) in patients 1, 4, and 11, and intravitreal methotrexate in patient 1. Five (42%) patients received no treatment.

Complete resolution of inflammatory lesions (AC cells, vitreous cells, angiographic retinal vasculitis, CME) was achieved in 5/6 (83%) patients with systemic treatment (patients 1, 4, 8, 11, and 12). Vitrectomy with silicone oil infusion for macular hole repair was performed in one (8%) patient; unfortunately, the surgery failed to close the macular hole.

As far as the different PUD categories were concerned, in total there were 6 (50%) PURPL patients, 2 (17%) PUOD patients, and 4 (33%) POSED patients.

Genetic testing

In total, genetic variants in IRD genes were reported in 11 (91%) patients. Six (50%) patients demonstrated VUS in IRD genes (*ABCC6*, *ADGRV1*, *CNGA3*, *CNGB1*, *IFT140*, *RP2*, *RPGR*, *TSPAN12*). Five (42%) patients had class 4 variants in IRD genes (*ABCC6*, *CRB1*, *GPR179*, *RHO*). Class 5 variants in IRD genes (*CNGA3*, *EYS*, *KCNV2*, *ZNF408*) were found in 4 (33%) patients. One patient had a negative panel result (no variants reported). Table 3 shows complete results of the genetic testing.

Genotype–Phenotype Correlation and Final Diagnosis After Genetic Testing

Three PURPL patients were diagnosed with IRD after genetic testing. Diagnoses were respectively *EYS*-related autosomal recessive RP (ARRP), *RHO*-related autosomal dominant RP (ADRP), and *CRB1*-related ARRP. One POSED patient (patient 9) was diagnosed with possible *RP2*-related X-linked RP (XLRP). Table 4 shows complete results of the genotype–phenotype correlation analysis and final diagnoses after genetic testing.

Selected Multimodal Imaging

Figure 1 shows the results of multimodal imaging for Cases 1, 3, 4, 7, 9, and 10.

Supplementary Information

Additional information on the cohort can be found in **Supplemental Digital Content 1** (see **Tables S1 and S2** http://links.lww.com/IAE/C394, http://links.lww.com/IAE/C395) in the supplement section.

Discussion

We performed genetic testing using a large IRD gene panel in this cohort of 12 PUD patients. Three (25%) patients could be reclassified as having an IRD after genetic testing. Patient 1 was diagnosed with *EYS*-related ARRP due to a homozygous pathogenic variant in the *EYS* gene, patient 2 was diagnosed with *RHO*-related ADRP caused by a heterozygous likely pathogenic variant in *RHO*, and patient 3 was diagnosed with *CRB1*-related ARRP due to compound heterozygous likely pathogenic variants in *CRB1*. All three patients belonged to the PURPL subgroup. Inflammatory features that led to misdiagnose these patients as uveitides were the presence of capillary leakage and intraretinal cystic spaces for patient 1; capillary leakage, intraretinal cystic spaces, and central choroidal neovascularization (CNV) for patient 2; and 1+ vitreous cells, capillary, and disc vessel leakage for patient 3.

As mentioned earlier, the presence of vitreous cells, vascular leakage, and intraretinal cystic spaces has been described in the context of IRD, particularly in cases of RP.[2–4] However, their presence opens up differential diagnostic issues with inflammatory disease, especially when these features are more severe than what is expected to be seen in RP, and when other signs of RP, such as intraretinal pigment migration, are very limited. In addition, with the currently more widely adopted use of ultra-widefield FA, peripheral vascular leakage detection in IRD patients will most probably be on the rise.[5] IRD and uveitis subspecialists alike must be aware of this possibility in order to rationalize diagnostic testing and to not overtreat these patients.

On another note, CNV development is exceptional in the context of IRD, except for some conditions in which it is well-known including Best disease, autosomal recessive bestrophinopathy, and Sorsby fundus dystrophy.[11,19] It has been rarely described in the context of RP as well,[20,21] but overall the presence of CNV in patient 2 was a major confounder, which delayed the diagnosis of RP.

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Table 3. Results of Genetic Testing

Patient, PUD Type	Genes	Genomic Coordinates*	Zygosity	HGVS Nomenclature	VC (ACMG/ ACGS)
1, PURPL	*EYS*	chr6:g.64388842T>C	hom	NM_001142800.1:c.5928-2A>G, p.(?)	5
2, PURPL	*RHO*	chr3:g.129533607G>A	het	NM_000539.3:c.937-1G>A, p.(?)	4
3, PURPL	*CRB1*	chr1:g.197429465A>C	het	NM_201253.2:c.2693A>C, p.(Asn898Thr)	4
	CRB1	chr1:g.197442200C>T	het	NM_201253.2:c.3913C>T, p.(Pro1305Ser)	4
4, PURPL	*KCNV2*	chr9:g.2718406C>T	het	NM_133497.3:c.667C>T, p.(Gln223Ter)	5
	TSPAN12	chr7:g.120856748A>C	het	NM_012338.3:c.16T>G, p.(Ser6Ala)	3
5, PURPL	—†	—	—	—	—
6, PURPL	*RPGR*	chrX:g.38286557_38286571del	het	NM_001034853.2:c.2447_2461del, p.(Gly816_Glu820del)	3
	CNGB1	chr16:g.57901551C>T	het	NM_001297.5:c.2869G>A, p.(Val957Ile)	3
7, PUOD	*CNGA3*	chr2:g.98396690A>G	het	NM_001298.2:c.1520A>G, p.(Asp507Gly)	3
8, PUOD	*ZNF408*	chr11:g.46703066C>T	het	NM_024741.3:c.475C>T, p.(Gln159Ter)	5
	IFT140	chr16:g.1524836C>T	hom	NM_014714.4:c.2945G>A, p.(Arg982Gln)	3
	ABCC6	chr16:g.16202006T>C	het	NM_001171.6:c.1171A>G, p.(Arg391Gly)	4
	ABCC6	chr16:g.16182422A>G	het	NM_001171.6:c.2237T>C, p.(Ile746Thr)	3
9, POSED	*RP2*	chrX:g.46853621T>C	hemi	NM_006915.2:c.248T>C, p.(Ile83Thr)	3
10, POSED	*ADGRV1*	chr5:g.90653628A>G	het	NM_032119.3:c.4054A>G, p.(Ile1352Val)	3
11, POSED	*GPR179*	chr17:g.38329638_38329639del	het	NM_001004334.3:c.3934_3935del, p.(Arg1312AlafsTer36)	4
12, POSED	*ABCC6*	chr16:g.16202006T>C	het	NM_001171.5:c.1171A>G, p.(Arg391Gly)	4
	CNGA3	chr2:g.98396490G>A	het	NM_001079878.1:c.1266G>A, p.(Trp422Ter)	5

*Based on GRCh38/hg38 assembly.
†A dash indicates negative panel results.
ACMG, American College of Medical Genetics; ACGS, Association for Clinical Genomic Science; hemi, hemizygous; het, heterozygous; HGVS, human genome variation society; hom, homozygous; POSED, posterior or panuveitis with established ophthalmological or systemic etiology and dystrophic features; PUD, posterior or panuveitis and dystrophic features; PUOD, idiopathic posterior or panuveitis with other dystrophic features; PURPL, idiopathic posterior or panuveitis with retinitis pigmentosa-like features; VC, variant category.

Moreover, it is interesting to note that none of the patients in whom we found granulomatous keratic precipitates ended up being diagnosed with definite IRDs. This could potentially point to granulomatous keratic precipitates being a helpful "rule out" finding in inflammatory IRD. However, it is important to remember that up to 1.2% of RP patients have typical findings of Fuchs heterochromic uveitis, which include diffuse pancorneal stellate keratic precipitates.[22]

A fourth patient (patient 9) could have potentially been reclassified as XLRP based on the presence of a hemizygous missense VUS (c.248T > C, p.[Ile83Thr]) in the *RP2* gene. However, the age of onset was rather atypical for *RP2*-related XLRP, considering that the patient started complaining of VF restriction at age 68 years. XLRP is often considered the most severe form of RP, and clinical signs usually appear much earlier, around the second decade of life.[23] However, it is possible that the patient compensated his visual deficit rather strongly, considering his presenting visual acuities were "hand motion" at 2 feet in both eyes. Moreover, the site of the missense variant in the *RP2* gene was compatible with known molecular mechanisms of *RP2*-related disease. Indeed, the majority of reported causal alterations are truncating variants, except in the cofactor C-like domain of the RP2 protein where pathogenic missense variants are

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Table 4. Genotype–Phenotype Correlation and Final Diagnosis After Genetic Testing

Pt	Genotype	Expected Phenotype (Inheritance Pattern)	Observed Phenotype	Genotype–Phenotype Correlation	Final Diagnosis
1	Hom splicing PV *EYS*	RP (AR)	Bilateral retinopathy sine pigmento with IF	Compatible	*EYS*-related ARRP
2	Het splicing LPV *RHO*	RP (AD, AR), CSNB, Riggs type (AD), RPA (AD, AR)	Bilateral paucipigmentary retinopathy with IF	Compatible	*RHO*-related ADRP
3	Comp het missense LPV *CRB1*	RP (AR), PPRCA (AD), LCA (AR)	Bilateral retinopathy sine pigmento with IF	Compatible	*CRB1*-related ARRP
4	Het nonsense PV *KCNV2* Het missense VUS *TSPAN12*	*KCNV2*: Cone dystrophy with supernormal rod ERG (AR) *TSPAN12*: FEVR (AD)	Bilateral paucipigmentary retinopathy with IF	Incompatible	—*
5	—	—	Bilateral paucipigmentary retinopathy with IF	NA	—
6	Het delins VUS *RPGR* Het missense VUS *CNGB1*	*RPGR*: RP (XL), CORD (XL), MD (XL) *CNGB1*: RP (AR)	Bilateral retinopathy sine pigmento with IF	Incompatible	—
7	Het missense VUS *CNGA3*	Achromatopsia (AR), COD (AR), CORD (AR)	Bilateral pigmentary retinopathy with inflammatory and dystrophic features	Incompatible	—
8	Het nonsense PV *ZNF408* Hom missense VUS *IFT140* Het missense LPV *ABCC6* Het missense VUS *ABCC6*	*ZNF408*: FEVR (AD), RP (AR) *IFT140*: RP (AR), short-rib thoracic dysplasia with or without polydactyly (AR) *ABCC6*: PXE (AR), GACI (AR), increased ischemic stroke risk (AD)	Unilateral granulomatous panuveitis with evolution toward unilateral retinopathy sine pigmento	Incompatible	—
9	Hemi missense VUS *RP2*	RP (XL)	Bilateral retinopathy sine pigmento with fundal hypopigmentation	Possibly compatible	Possible *RP2*-related XLRP
10	Het missense VUS *ADGRV1*	Usher syndrome, type 2C (AR), familial febrile seizures (AD)	Bilateral posterior uveitis with concentric midperipheral dystrophic changes	Incompatible	—
11	Het delins LPV *GPR179*	cCSNB (AR)	Bilateral panuveitis with dystrophic changes	Incompatible	—
12	Het missense LPV *ABCC6* Het nonsense PV *CNGA3*	*ABCC6*: PXE (AR), GACI (AR), increased ischemic stroke risk (AD) *CNGA3*: Achromatopsia (AR), COD (AR), CORD (AR)	Unilateral panuveitis with dystrophic changes	Incompatible	—

*A dash indicates no change in diagnosis after genetic testing or negative panel results.

AD, autosomal dominant; AR, autosomal recessive; COD, cone dystrophy; Comp, compound; CORD, cone-rod dystrophy; c, complete; CSNB, congenital stationary night blindness; ERG, electroretinogram; FEVR, familial exudative vitreoretinopathy; GACI, generalized arterial calcification of infancy; Het, heterozygous; Hom, homozygous; IF, inflammatory features; LCA, Leber congenital amaurosis; LPV, likely pathogenic variant; MD, macular dystrophy; NA, not applicable; PPRCA, pigmented paravenous retinochoroidal atrophy; Pt., patient; PV, pathogenic variant; PXE, pseudoxanthoma elasticum; RP, retinitis pigmentosa; RPA, retinitis punctata albescens; VUS, variant of unknown significance; XL, X-linked.

more frequent.[23] The p.Ile83Thr change is located within this domain. As such, this case could be considered a possible *RP2*-related XLRP, increasing the number of diagnostic reclassifications to 4/12 (33%) patients. Unfortunately, no living female relative was available for clinical assessment of lyonization and segregation analysis of the variant. There were no other affected males in the family of patient 9.

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Seven (58%) patients had variants in IRD genes that could not explain their phenotype because the variants were of unknown significance, or the identified variants were located in genes that did not match the clinical presentation, or individuals were heterozygous for variants in autosomal recessive IRD genes. This is an important finding of our work clearly indicating that gene testing in uveitis patients must be performed in a multidisciplinary approach, involving clinicians with ophthalmic genetics expertise.

Overall, the presence of nyctalopia was an excellent clinical indicator of RP in this cohort, as 3/4 (75%) patients with nyctalopia were ultimately molecularly diagnosed with RP.

We suggest a clinical decision support algorithm (Figure 2) to aid clinicians in deciding which patients could potentially benefit from whole-exome sequencing testing in cases of posterior or panuveitis with or without RPL dystrophic features.

In a study investigating six IRD cases that were initially misdiagnosed as intermediate uveitis, three patients had *CRB1*-related ARRP, one patient had both heterozygous *PRPF31* and *SNRNP200* missense variants, entailing a dual diagnosis of *PRPF31*- and *SNRNP200*-related ADRP, one patient had *USH2A*-related ARRP, and the final patient had *RP1*-related ARRP.[3] All patients initially presented with reduced VA and one patient complained of nyctalopia. Patients had minimal or no anterior segment inflammation, 1+ to 3+ vitreous cells, and CME was present in all patients. Fluorescein angiogram was performed in four patients and showed optic disc or macular leakage in three. All patients, but one, were treated for CME with immunomodulatory drugs ranging from oral corticosteroids to cDMARDs and bDMARDs, to no avail. Patients also received periocular or intraocular corticosteroid injections, which helped temporarily improve CME in three patients. Interestingly, acetazolamide was used in four patients with no lasting benefit on CME. Median follow-up before IRD diagnosis was 6 years (1–8 years). The investigators performed genetic testing because of nyctalopia (3 patients), progressive VF defects (4 patients), and abnormal ERGs (all patients).

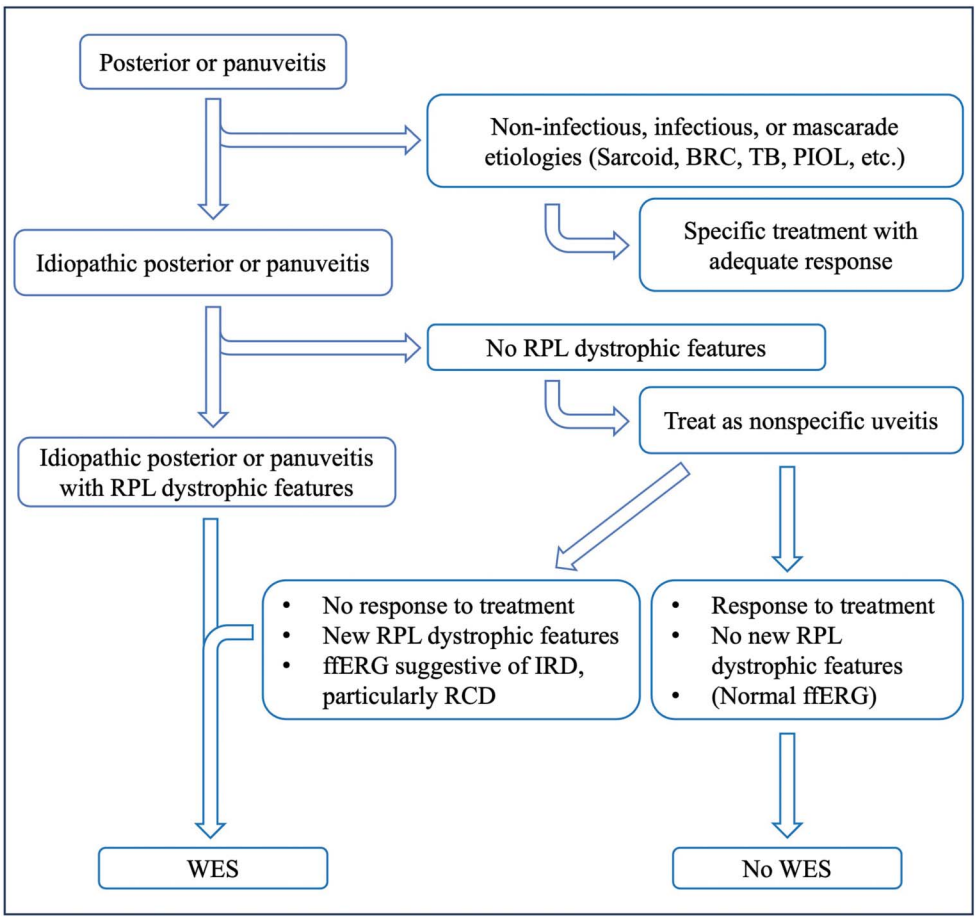

Fig. 2. Clinical decision support algorithm for performing whole-exome sequencing in posterior or panuveitis with or without RP-like dystrophic features. First, rule out non-infectious, infectious, and mascarade etiologies such as sarcoidosis, birdshot retinochoroiditis, tuberculosis, or primary intraocular lymphoma. If a specific uveitis diagnosis is made, initiate specific treatment and expect an adequate treatment response. If a diagnosis of idiopathic posterior or panuveitis is made, look for RP-like dystrophic features such as peripheral intraretinal pigment clumping, midperipheral retinal atrophy, perifoveal or perimacular hyperautofluorescent rings on blue light autofluorescence, and perifoveal ORA on macular SD-OCT. If there are none, treat as you would nonspecific uveitis. If the patient responds to treatment, no new RPL dystrophic features develop during the follow-up, and a full-field electroretinogram is normal (optional), do not perform whole-exome sequencing. If RP-like dystrophic features are present from the beginning or they develop during the follow-up, if the patient does not respond to treatment, or a full-field electroretinogram is suggestive of inherited retinal disease, particularly rod-cone dystrophy (rod greater than cone dysfunction), perform whole-exome sequencing.

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The authors recommend keeping a high degree of awareness of these genetic masqueraders of uveitis and advise clinicians to use appropriate investigations (VF, ERG, WES-based genetic testing) in the case of IRD suspicion in young patients with intermediate uveitis and CME.[3]

One single other study in which WES-based genetic testing was systematically performed in cases of uveitis was found.[24] The study investigated 164 cases of intermediate, posterior, or panuveitides, collectively grouped as posterior segment uveitides. However, the authors did not target their analysis toward IRD. Rather, they searched for an association between variants within the exome and posterior segment uveitis. Classic Mendelian uveitic entities like Blau syndrome resulting from heterozygous *NOD2* pathogenic variants or autosomal dominant neovascular inflammatory vitreoretinopathy caused by heterozygous *CAPN5* pathogenic variants were found. They also found associations with variants in genes implicated in innate immune signaling pathways such as the NOD-like receptor family genes, e.g., *NLRP1*, *NLRP3,* and *NLRC4*, or *TYK2*, which encodes an intracellular tyrosine kinase involved in the JAK-STAT pathway. An association was also found with adaptive immune system genes like *PTPN22*, which encodes a regulator of T-cell activity. Interestingly, variants were identified in three Usher syndrome genes, namely *USH2A*, *ADGRV1*, and *CDH23*. Unfortunately, the authors did not comment on this finding, and it is not known whether these variants were heterozygous, compound heterozygous, or homozygous. However, it suggests a possible association of these genes with posterior segment uveitis, or alternatively, if the variants were biallelic, that some of the cases included in this cohort were in fact IRDs.

This study has limitations, the first of which is the small number of patients included in our cohort. Combining PUD patients from many different groups could be an approach to overcome this limitation, provided all patients have been seen by experienced specialists in uveitis and IRD. Second, retrospective studies are subject to inherent limitations and biases. Some potential PUD cases had to be excluded from analysis because of incomplete data availability. Third, there are potential limitations associated with the genetic testing strategy that we followed. Most noncoding pathogenic changes with an effect on splicing or regulation are missed by the approach we used, i.e., exome-sequencing-based panel testing. Also, complex structural variants may have been missed using an exome-based approach. In cases where only one heterozygous (likely) pathogenic variant was found, further whole-genome sequencing would be useful.

Conclusions

In this cohort of 12 patients with PUD, 3 (25%) patients were reclassified as having IRD following gene panel testing. It is possible that a fourth patient also suffered from an IRD. All three molecularly resolved cases belonged to the PURPL subgroup, bringing the overall genotype resolve rate in that subgroup to 50%. We recommend performing gene panel testing in every PURPL patient, particularly in the presence of nyctalopia, to avoid overlooking undiagnosed IRDs. This is particularly important because patients benefit from confirmed IRD diagnoses in many ways such as better understanding the prognosis of their disease, getting access to family cascade testing, potentially benefiting from novel therapies, and receiving practical and economic supports.

Key words: genetic testing, inherited retinal disease, panuveitis, posterior uveitis, retinitis pigmentosa, rod-cone dystrophy, uveitis masquerade syndrome, whole exome sequencing.

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