TOP IRDS TO WATCH:
RETINITIS PIGMENTOSA

Here's what you need to diagnose, counsel, and follow patients with the most common inherited retinal disease.

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Retinitis pigmentosa (RP) is the most common form of inherited retinal disease (IRD), affecting approximately one in 4,000 individuals worldwide.[1]

RP is inherited in autosomal dominant, autosomal recessive, or X-linked patterns, with onset typically occurring in adolescence or early adulthood. It presents with nyctalopia, followed by progressive constriction of the field of vision and then, in severe cases, complete blindness. Classic fundoscopic findings include bone-spicule pigmentation, attenuated retinal vessels, and waxy pallor of the optic disc (Figure 1). As the disease progresses, posterior subcapsular cataract, cystoid macular edema (CME), and epiretinal membranes (ERM) may develop, contributing to further vision loss.

DIAGNOSTIC PEARLS

The diagnosis of RP involves history, fundus examination, imaging, functional testing, and molecular genetics.

Spectral-domain OCT assists in evaluating ellipsoid zone (EZ) integrity and detecting complications such as CME and ERM (Figure 2). Full-field electroretinography remains the standard for functional testing, often revealing severely diminished or absent rod and cone responses.

Fundus autofluorescence (FAF) is a critical noninvasive tool that often reveals a hyperautofluorescent ring in the macula that represents the transition zone between the healthy and the degenerating retina (Figure 3).

After analyzing FAF images across 11 genotypes of RP, we identified eight distinct autofluorescence patterns—four within the macula (eg, central foveal hyperautofluorescence, bull's-eye patterns) and four in the extramacular retina (eg, midperipheral rings, patchy or diffuse hypoautofluorescence).[2] While certain features such as double concentric hyperautofluorescent rings were once considered pathognomonic (eg, *NR2E3*), this study found them in other genotypes as well, including *RHO*, *RPGR*, and *USH2A*-linked RP. These findings suggest FAF is valuable for

AT A GLANCE

- Retinitis pigmentosa (RP) is the most common form of inherited retinal disease, affecting approximately one in 4,000 individuals worldwide.
- Classic fundoscopic findings in RP include bone-spicule pigmentation, attenuated retinal vessels, and waxy pallor of the optic disc.
- Although there is no cure for most forms of RP, management focuses on visual rehabilitation, monitoring for treatable complications, and preserving quality of life.
- The therapeutic landscape for RP is rapidly evolving, and several clinical trials show promise.

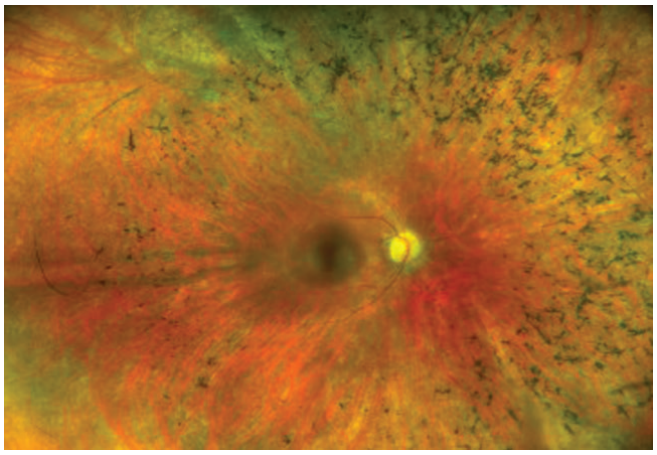

Figure 1. Patients with RP often present with bone-spicule pigmentation, loss of peripheral retinal vessels, and vascular attenuation.

documenting disease severity and progression but is not reliable for distinguishing specific genotypes.

Ultra-widefield (UWF) fundus photography and autofluorescence are becoming important tools in the diagnosis and follow-up of RP. In a study using UWF fundus imaging, we found that RP patients had significantly fewer peripheral retinal vessels compared with controls, with 22% of eyes completely lacking vessels in the far periphery. These findings highlight that symmetrical peripheral vessel dropout is a relatively constant feature of RP, which—after retinal bone-spicule pigmentation—may be the most recognizable characteristic on UWF imaging, surpassing more subjective signs such as vascular attenuation and waxy disc pallor.[3]

GENETIC TESTING

RP has been associated with mutations in more than 100 genes.[4] Identifying the causative mutation provides valuable prognostic information, clarifies inheritance patterns, and is increasingly necessary for clinical trial eligibility and consideration of investigational gene therapy treatments.

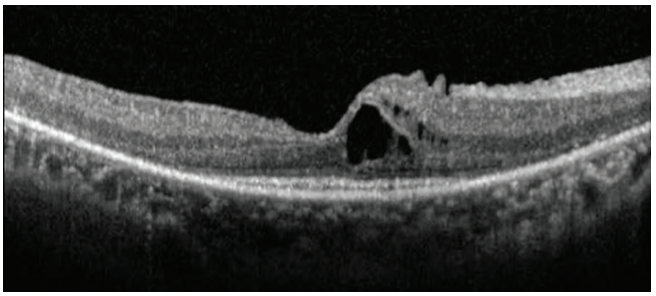

Figure 2. OCT imaging of a patient with RP reveals the loss of the EZ and outer nuclear layer outside the fovea, as well as CME and ERM.

The gene panels vary among laboratories. Our recent study compared the genetic testing reports of Invitae and Blueprint Genetics in 216 patients with IRD, including RP, and found major differences between the two labs.[5] Interestingly, among the seven patients tested by both laboratories, none had identical reported gene variants, even when the mutations were in genes present on both testing panels. These findings highlight the importance of carefully interpreting genetic testing results and considering the variability between testing platforms.

LONG-TERM MANAGEMENT AND COMPLICATIONS

Management focuses on visual rehabilitation, monitoring for treatable complications, and preserving quality of life. CME occurs in 18% to 50% of RP patients and can often be managed with topical and/or systemic carbonic anhydrase inhibitors.[6,7] Other cases may respond to topical NSAIDs or topical, periocular, or intravitreal steroids. Cataract, especially posterior subcapsular opacities, is common and may require surgical intervention in visually significant cases.

Currently, no vitamin or supplement clearly benefits patients with RP. While high-dose vitamin A supplementation was previously reported to slow disease progression in RP based on a large clinical trial,[8] a recent reanalysis of the same trial concluded that vitamin A supplementation does not slow the progression of RP.[9] Furthermore, vitamin A may pose risks to patients with liver disease, renal transplant history, or osteopenia.[10,11]

A phase 1 study showed that oral N-acetylcysteine (NAC), a compound that reduces oxidative stress, administered for 6 months was well-tolerated and resulted in small but statistically significant improvements in visual acuity and light sensitivity.[12] Currently, a phase 3 multicenter, randomized clinical trial evaluating the efficacy and safety of oral NAC in RP patients is underway.[13] If successful, NAC may become a viable therapy option for patients with RP.

Finally, low vision services, orientation and mobility training, and psychosocial support are essential for patients coping with vision loss.

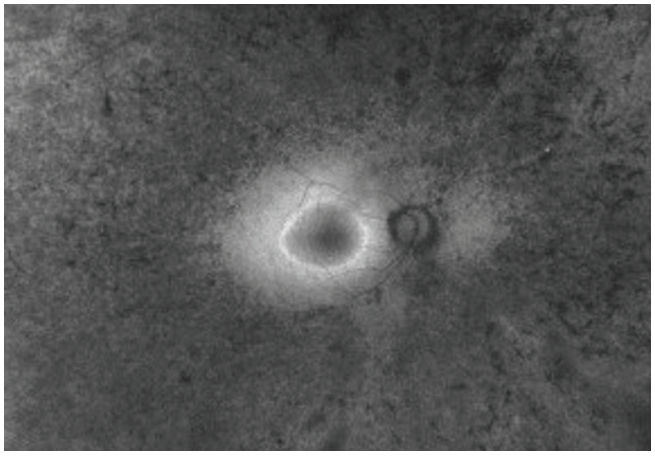

Figure 3. FAF of a patient with RP shows a macular hyperautofluorescent ring and peripheral hypoautofluorescence.

MONITORING PROGRESSION AND TREATMENT RESPONSE

Monitoring RP involves both functional and structural modalities. While visual field testing, particularly kinetic perimetry, has been a valuable tool in evaluating peripheral vision loss and disease trajectory, it is prone to operator variability and is difficult to compare.[14,15]

Microperimetry enables precise mapping of retinal sensitivity and can detect progression even when visual acuity remains stable.[16] EZ length, visualized on OCT, reflects photoreceptor integrity and correlates well with visual function, making it a useful biomarker of progression.[17] Full-field stimulus threshold testing provides a global sensitivity measure, making it feasible to measure treatment response even in advanced disease without fixation and severely limited visual fields.[18] The multi-luminance mobility test evaluates navigational ability under different lighting conditions and is used as a meaningful outcome measure in gene therapy trials.[19]

Low-luminance visual acuity detects central visual deficits not captured by standard acuity testing and is increasingly recognized as a sensitive endpoint in early-stage disease.[20]

CLINICAL PIPELINE

The therapeutic landscape for RP is rapidly evolving. Voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics), the first FDA-approved gene therapy for *RPE65*-associated retinal dystrophy, represents a major breakthrough.[21] A 2022 analysis of 101 gene therapy clinical trials targeting IRDs showed RP as the most studied condition with 39 trials.[22] Common targets include *RPE65*, *ND4*, and *REP1*, with 77 trials using gene augmentation strategies and adeno-associated viral vectors in 90% of cases.

On the horizon, two phase 3 trials show promise: the LUMEOS trial of AAV5-hRKp.RPGR (Janssen) targeting *RPGR* and the gene agnostic liMeliGhT trial of OCU400-301 (Ocugen), which targets *NR2E3*.[23,24] If successful, these therapies could bring viable treatment options to the market in the near future, representing the next generation of mutation-specific and mutation-agnostic gene therapies.

RP remains a leading cause of inherited blindness. With advances in diagnostics and emerging treatment on the horizon, there is real hope for improving the outlook of patients living with this condition. ■

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