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A Case Series of Occult Macular Dystrophy

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Abstract

Purpose. This case series showcases three patients with mild variation in phenotypic presentations of Occult Macular Dystrophy (OCMD), an autosomal-dominant inherited retinal dystrophy (IRD) associated with a retinitis pigmentosa-1-like-1 (*RP1L1*) gene mutation. All cases have confirmed *RP1L1* gene mutations and display a range of phenotypic expressions on various imaging modalities and visual acuities.

Material and Methods. Three patients of the University Eye Center (UEC) with confirmed *RP1L1* gene mutations presented for follow-up or baseline imaging to rule out inherited retinal disease. All patients underwent fundus photography with and without fundus autofluorescence (FAF), optical coherence tomography (OCT), genetic testing, visual fields, and electrodiagnostic testing such as multifocal electroretinogram (mfERG) and/or full-field electroretinogram (ffERG).

Results. In two of the three cases, minimal to no funduscopic changes are appreciated on ophthalmoscopy or fundus photography with and without FAF. Effects of OCMD can only be appreciated on OCT imaging, including attenuation or disruption of the photoreceptor integrity line (PIL), and central depression on visual field testing. One of the three cases displays an unusual presentation with asymmetric central outer retinal atrophy that can be appreciated on fundoscopy as well as other imaging modalities.

Conclusion. Although individuals with this IRD typically funduscopically appear normal, there may be a phenotypic spectrum impacting visual potential. Diagnosis of this condition is heavily dependent on macular OCT, electrophysiological testing, and genetic testing.

Keywords

Occult Macular Dystrophy, *RP1L1,* inherited retinal disease, electroretinogram, OCT

Introduction

Occult macular dystrophy (OCMD) is an uncommon autosomal dominant inherited retinal dystrophy (IRD) affecting macular cone function.[1] This dystrophy results from a mutation in the retinitis pigmentosa-1-like-1 (*RP1L1*) gene, which encodes a protein specific to photoreceptors.[2,3] OCMD, otherwise referred to as Miyake's disease, was first characterized in 1989 by Yozo Miyake as progressive central vision loss with normal funduscopic appearance, fluoresceine angiography, and full-field electroretinogram (ffERG).[4] Prevalence and patient demographic of this disease are is still unclear.[5] A higher prevalence in Eastern Asian patients has been suggested, as most studies have been based on this population.[5,6] However, epidemiological conclusions cannot be determined due to relatively small number of reported cases and research on this disease as well as likely heightened awareness and screening protocols in these regions.[5] The age of vision loss can significantly vary from 6 to 60 years old and vision may progressively decrease from 10 to 30 years.[1,7] Because of the occult nature of this condition, multimodal imaging is key to diagnosis, with emphasis of optical coherence tomography (OCT) to visualize subtle outer retinal changes and focal or multifocal electroretinograms (mfERG) to measure central photoreceptor functioning. Further imaging, such as visual fields to monitor for progression overtime and fundus autofluorescence to rule out other maculopathy, can be useful.[8-14]

This case series describes three patients with mild variations in phenotypic presentation of OCMD With confirmed mutations in the *RP1L1* gene. Although this condition typically displays no fundoscopic or fundus auto-fluorescence (FAF) abnormalities and is often identified using OCT, these cases display a range of fundus findings and visual acuity.

Case 1

62-year-old black female referred for electrodiagnostic testing to rule out Stargardt's Disease. The patient had a history of cataract surgery one year prior and reported reduced vision at distance and near. She denied a history of reduced vision as a child, color vision deficits, nyctalopia, or family history of vision loss secondary to inherited diseases. She had a history of hypertension for ten years, controlled with two medications, and pre-diabetes mellitus for one year that was not treated with medications.

Her best corrected visual acuity (BCVA) was 20/125 OD and 20/80 OS. External testing and anterior segment exam were unremarkable. Dilated fundus examination displayed distinct optic nerve margins with healthy neuroretinal rim appearance, flat and in-tact macula, healthy vessel appearance and caliber (**figure 1**, top), and attached peripheral retina 360-degrees OU with binocular indirect ophthalmoscopy.

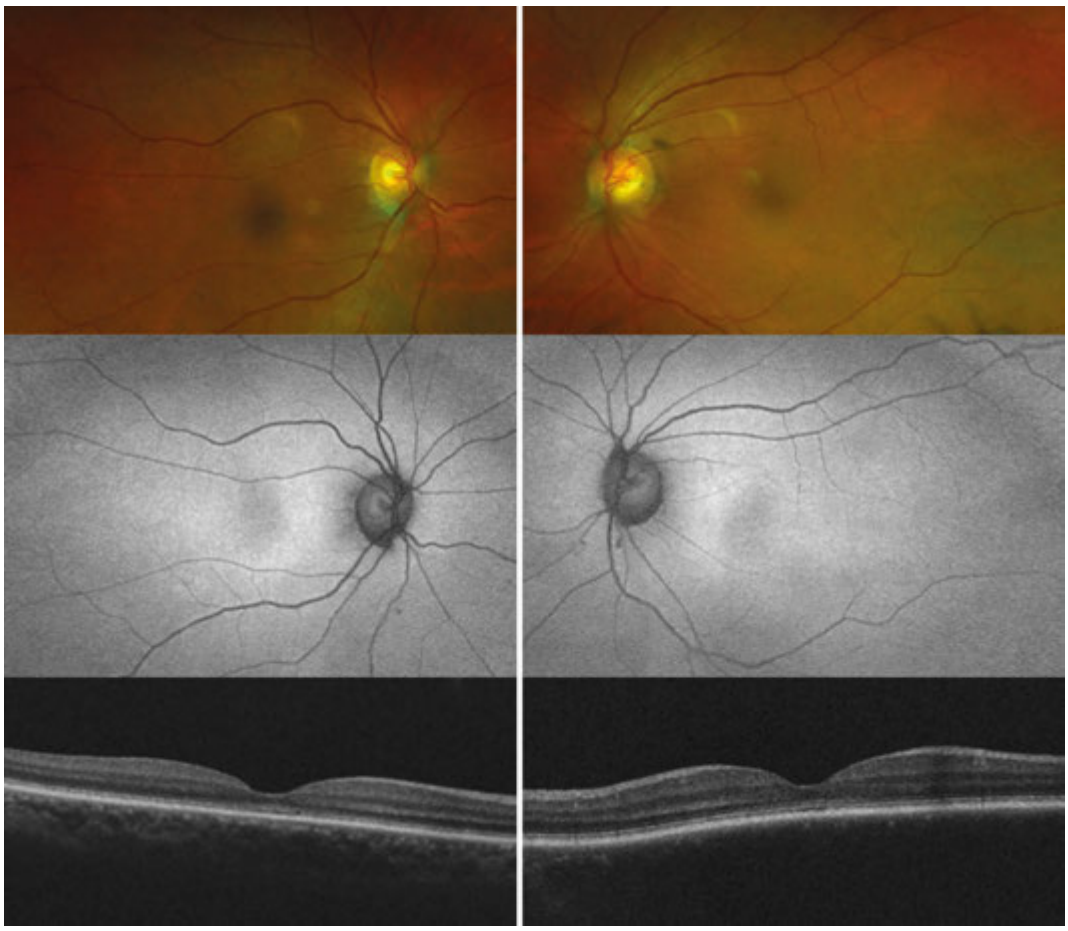

Figure 1: *Case 1 – Optos fundus photos of the right and left eye (top), Optos fundus photos with FAF of the right and left eye (middle), and Cirrus OCT macular raster scans of the right and left eye (bottom).*

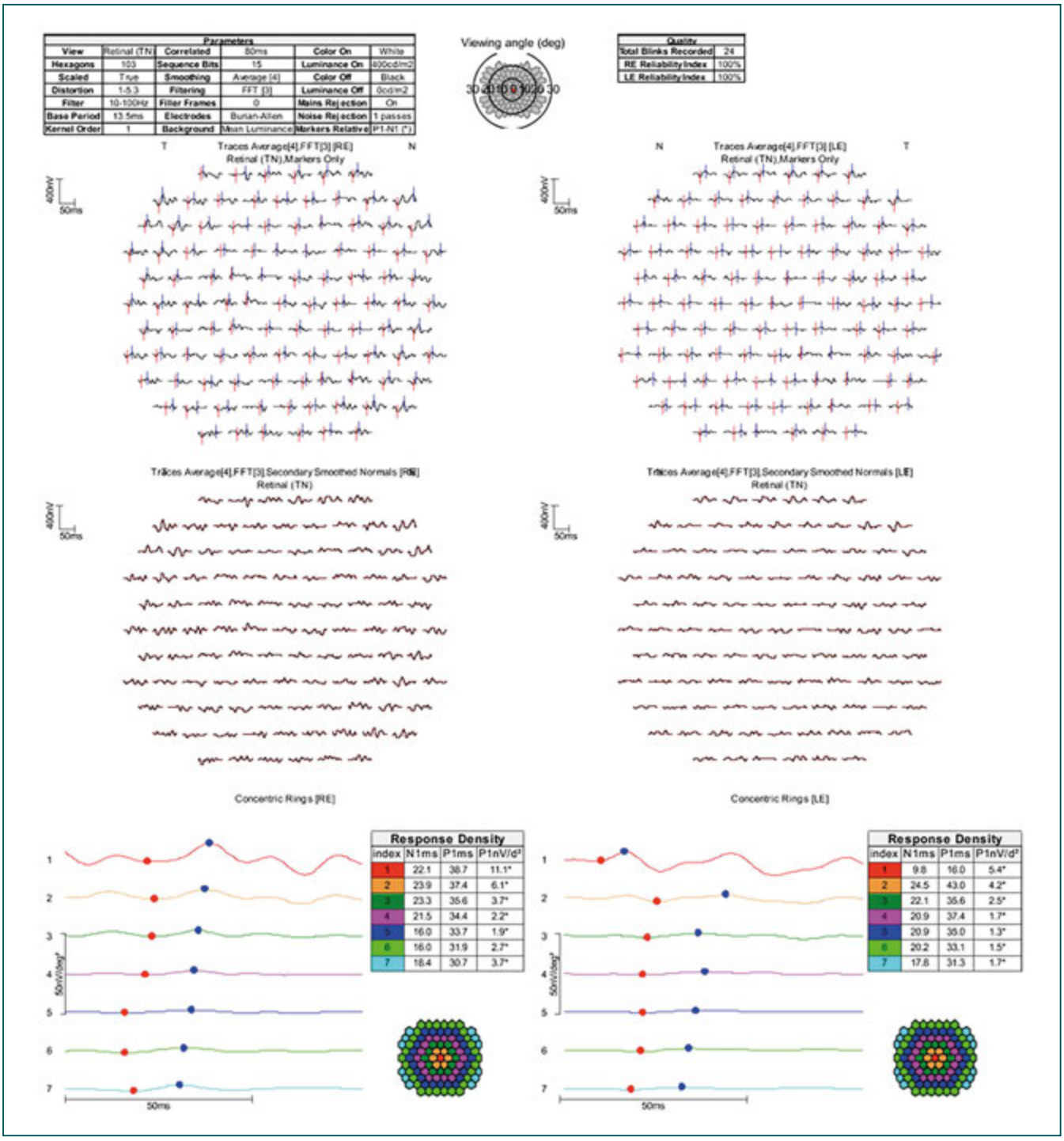

Figure 2: Case 1 – Diagnosys mfERG of the right eye (left) and left eye (right).

Her fundus photos with FAF showed trace hyperautofluorescence (AF) surrounding the macula, otherwise unremarkable (figure 1, middle). The hyperAF suggests the potential for stressed retinal pigment epithelium (RPE) cells surrounding the macula, however likely normal functioning. The macular OCT displayed normal foveal contour, no macular edema, and no inner or outer retinal atrophy OU. Diffuse thinning and mild photoreceptor integrity line (PIL) attenuation and disruption were noted sub-foveally OU (figure 1, bottom), consistent with her reduced central vision. The multifocal mfERG showed diffusely depressed outer retinal responses, worse centrally OU and worse in the left eye compared to the right eye (figure 2). The Octopus M-Top visual field revealed decreased sensitivity centrally, greater in the right eye. The defects are inferotemporal to fixation OD and nasal to fixation OS. The slightly off-center location of these defects suggests bilateral eccentric fixation, which is commonly seen in inherited macular dystrophies (figure 3). The results of the mfERG and the visual field generally coincide in that there is reduced outer retinal function and decreased

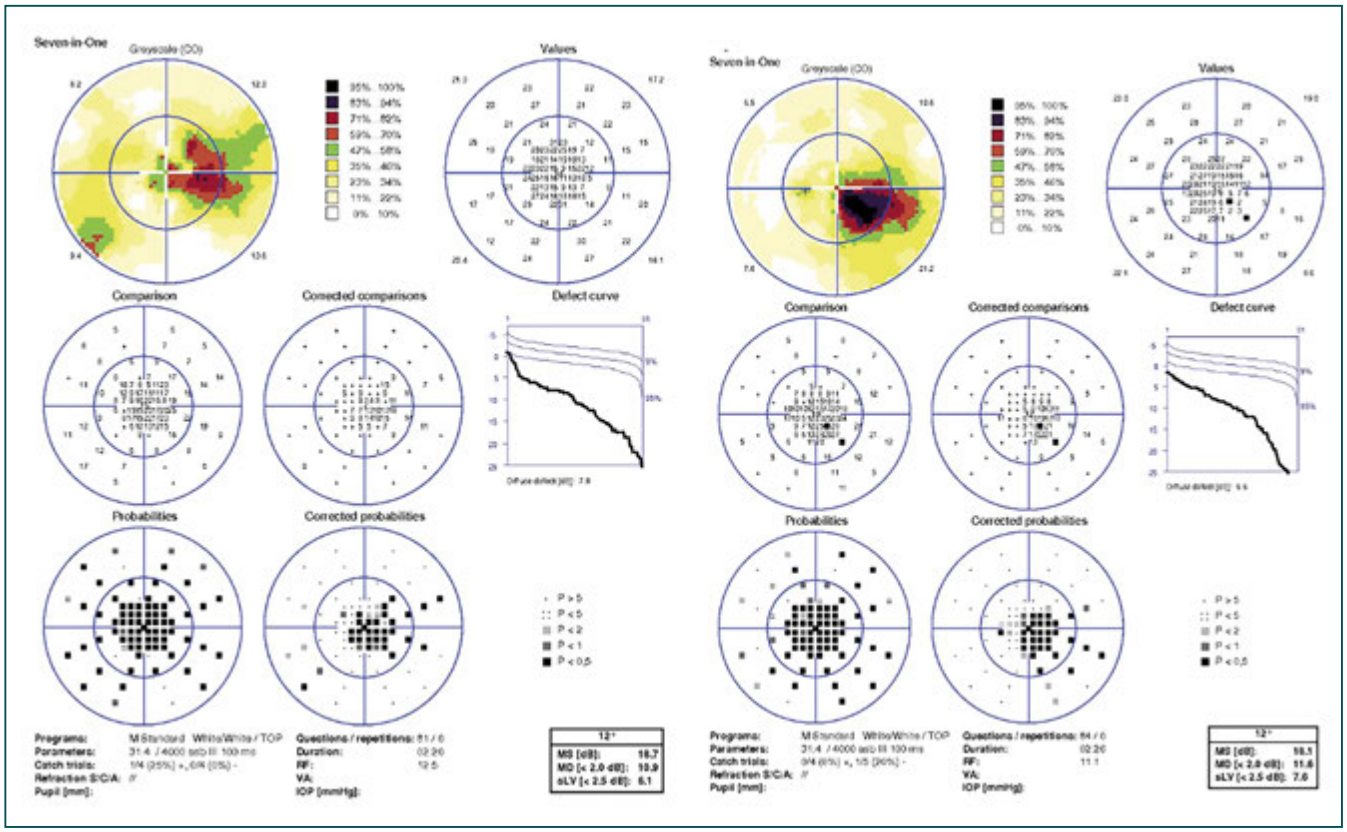

Figure 3: Case 1 – Octopus M-TOP visual fields of the left eye (left) and right eye (right).

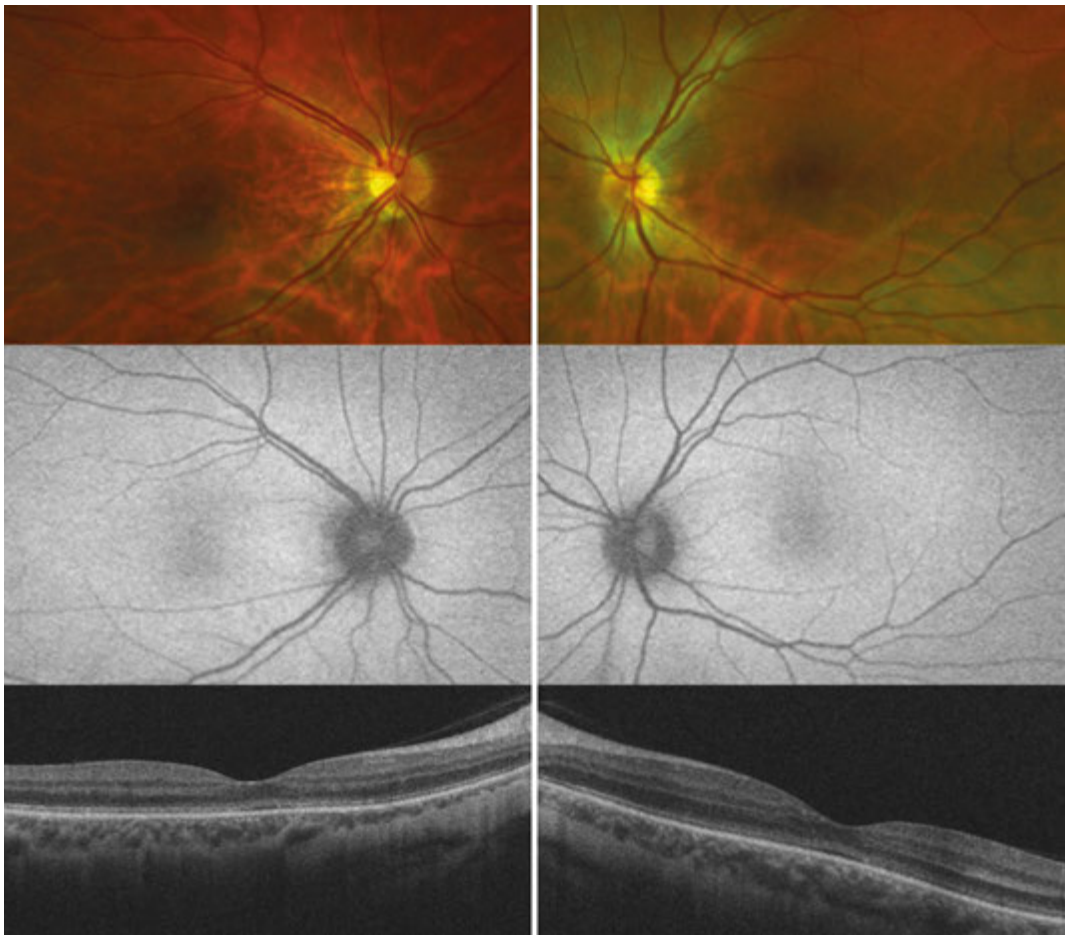

Figure 4: Case 2 – Optos fundus photos of the right and left eye (top), Optos fundus photos with FAF of the right and left eye (middle), and Cirrus OCT macular raster scans of the right and left eye (bottom).

sensitivity centrally in both eyes. However, the visual field and visual acuity suggest more advanced disease in the right eye whereas the mfERG suggests the opposite. Repeat testing in the future may be considered to confirm asymmetry of the disease process.

Genetic testing was performed using Next Generation Sequencing after obtaining a buccal sample analyzed by Invitae, Inc. Results revealed one pathogenic variant identified in *RP1L1,* one pathogenic variant in PCARE, which is associated with autosomal recessive retinitis pigmentosa, and four other additional variants of uncertain significance.

Case 2

35-year-old Italian male with a history of OCMD and high myopia OU presented for a follow-up. The patient's vision had been reduced since 12 years of age and denied any changes

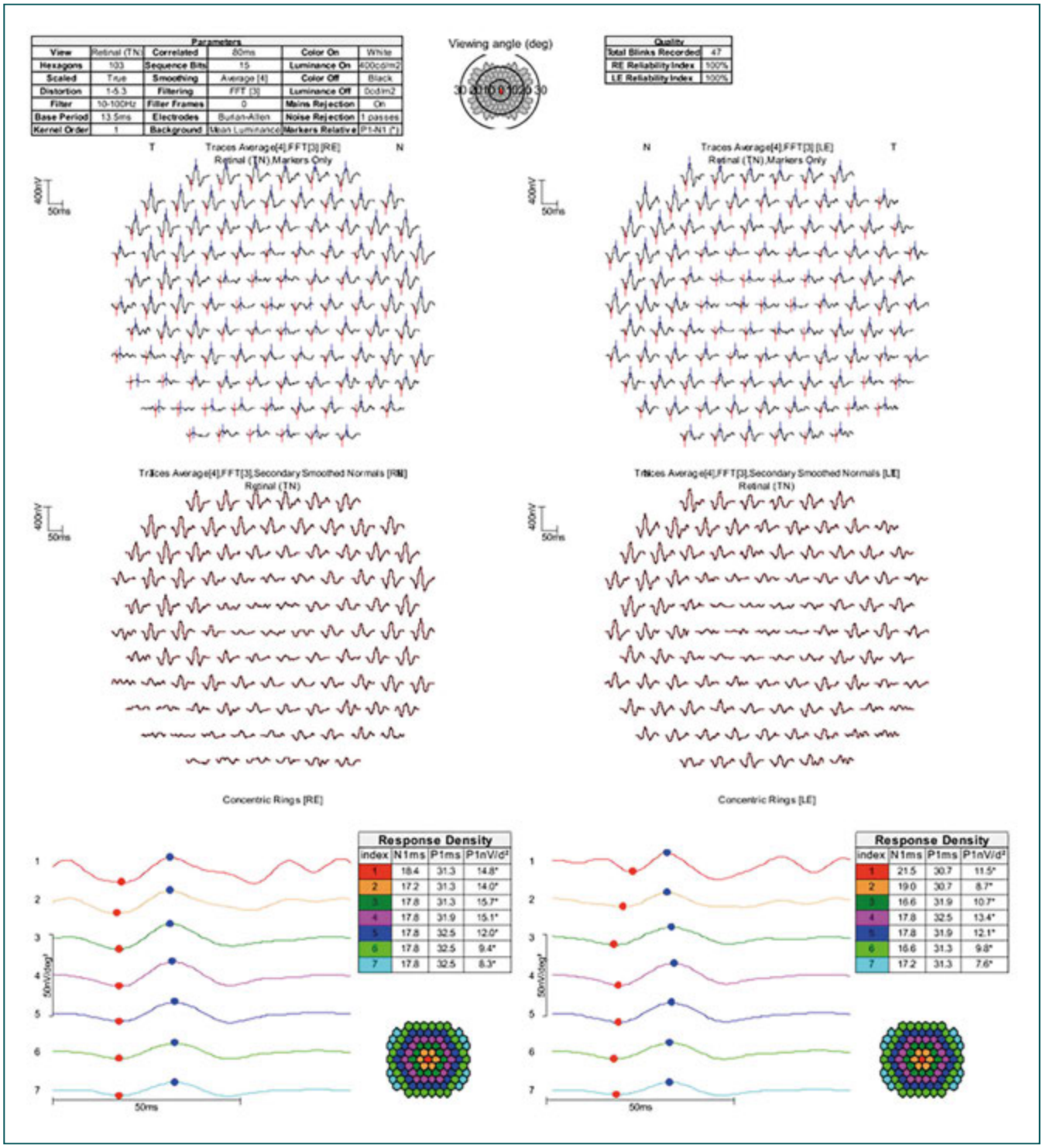

Figure 5: Case 2 – Diagnosys mfERG of the right eye (left) and left eye (right).

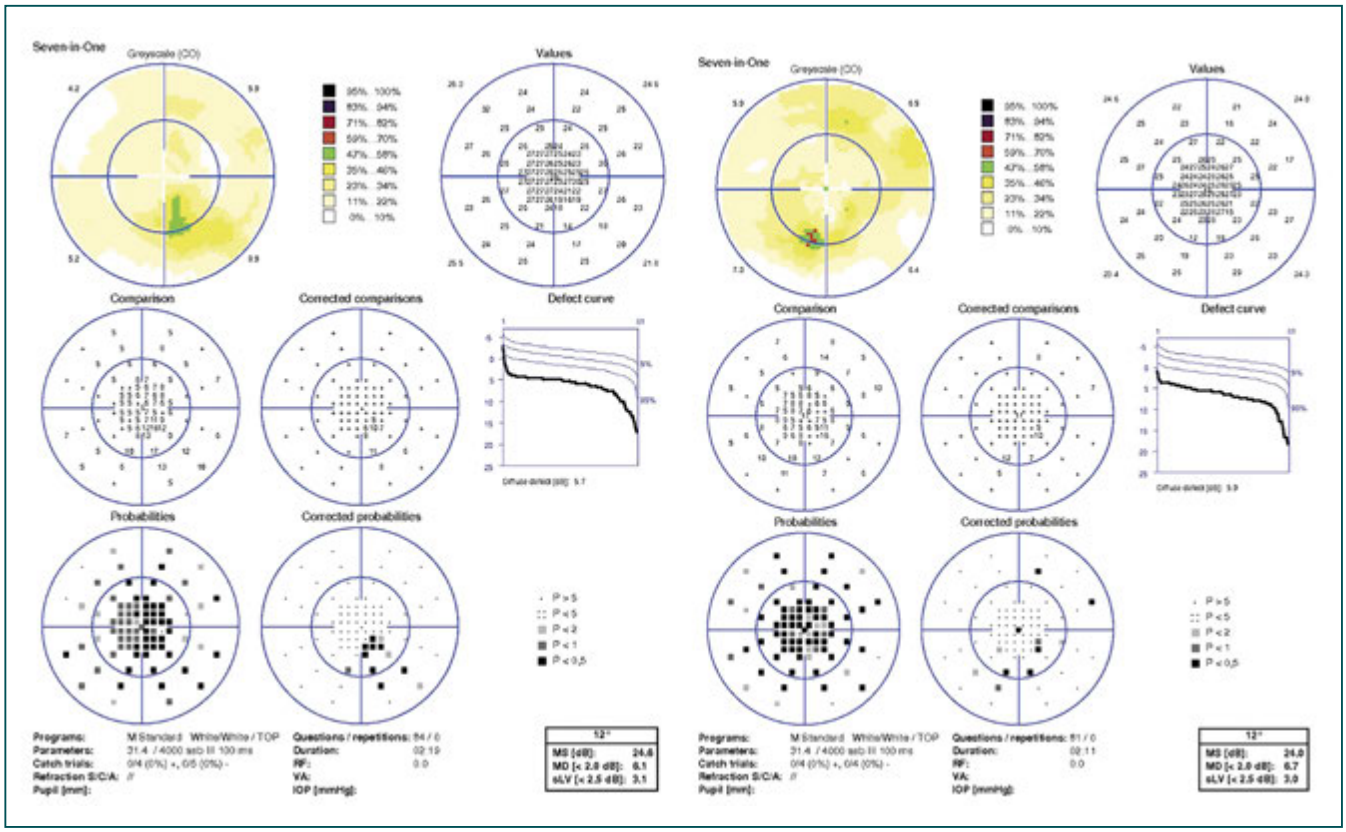

Figure 6: Case 2 – Octopus M-TOP visual fields of the left eye (left) and right eye (right).

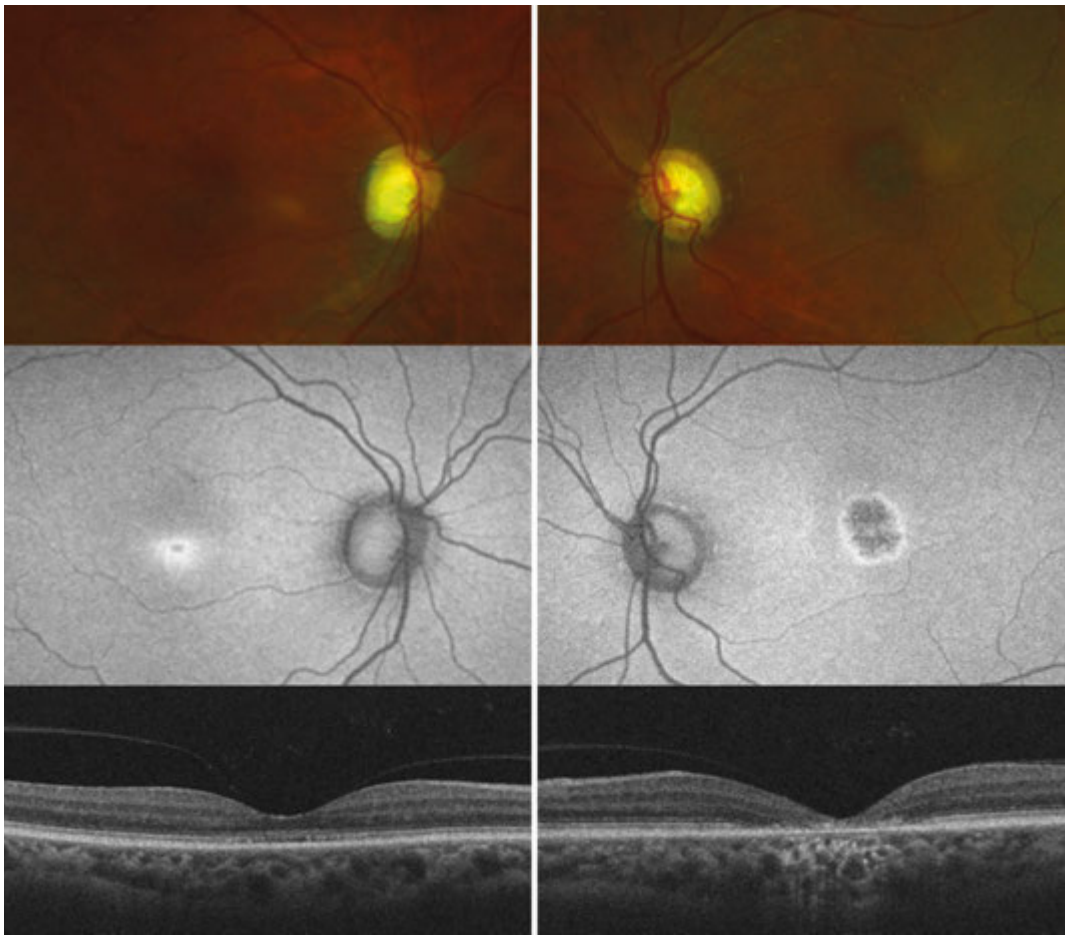

Figure 7: Case 3 – Optos fundus photos of the right and left eye (top), Optos fundus photos with FAF of the right and left eye (middle), and Cirrus OCT macular raster scans of the right and left eye (bottom).

in vision since his previous eye exam. His medical history was unremarkable, and he was not on any medications. He had a positive family history of OCMD including his brother and mother.

His BCVA is 20/80 OD/OS. External testing and anterior segment exam were unremarkable OU. Dilated fundus exam displayed distinct optic nerve margins with healthy neuroretinal rim appearance and a mild myopic tilt, healthy vessel appearance and caliber, flat and in-tact macula with a positive foveal reflex (**figure 4**, top), and attached peripheral retina 360-degrees with mild white-without-pressure OU on binocular indirect ophthalmoscopy.

The macular OCT displayed normal foveal contour, no macular edema, and no inner or outer retinal atrophy OU. The fundus photos with FAF were unremarkable OU, (**figure 4**, middle) and mild photoreceptor PIL attenuation and disrup-

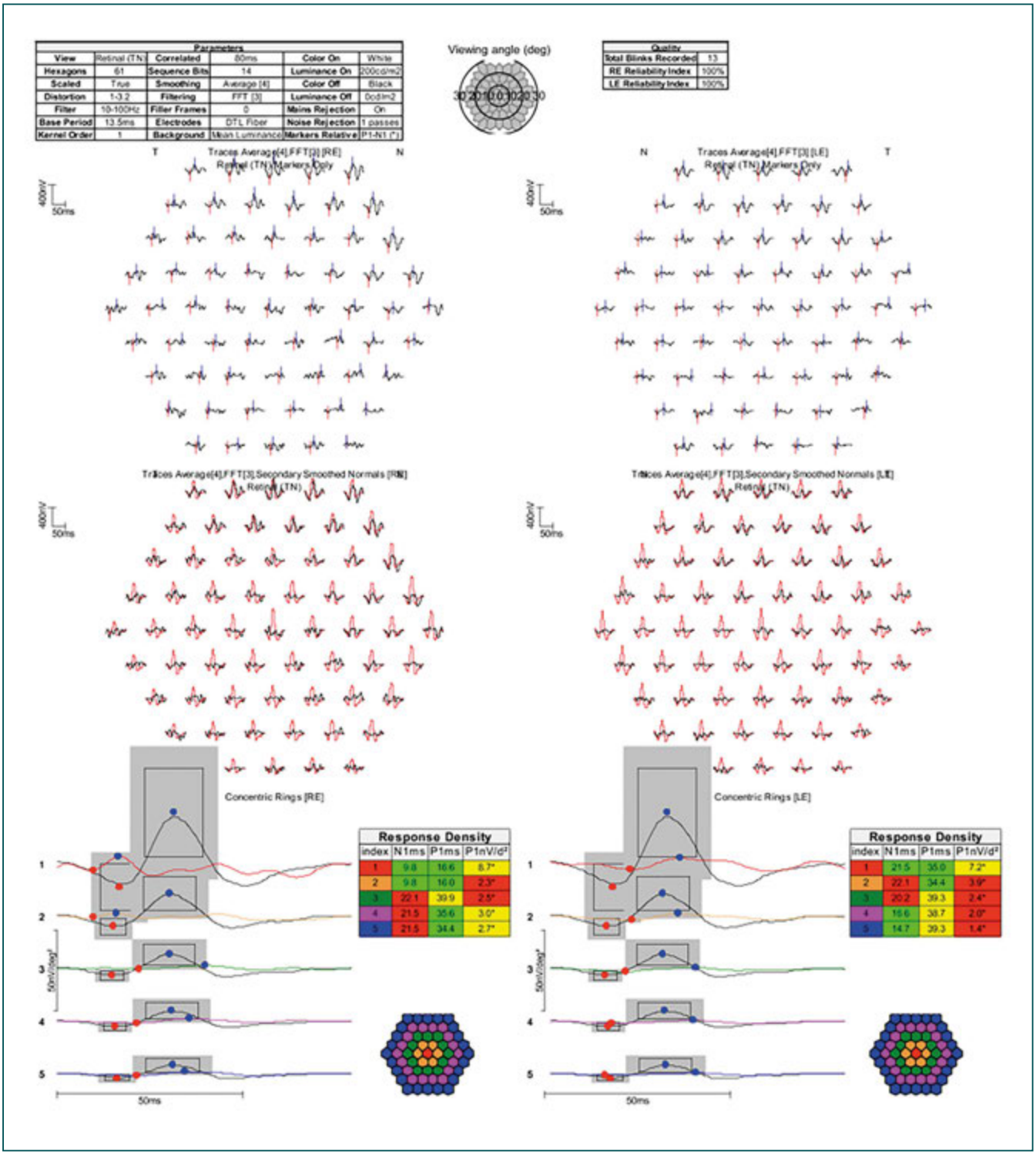

Figure 8: Case 3 – Diagnosys mfERG of the right eye (left) and left eye (right).

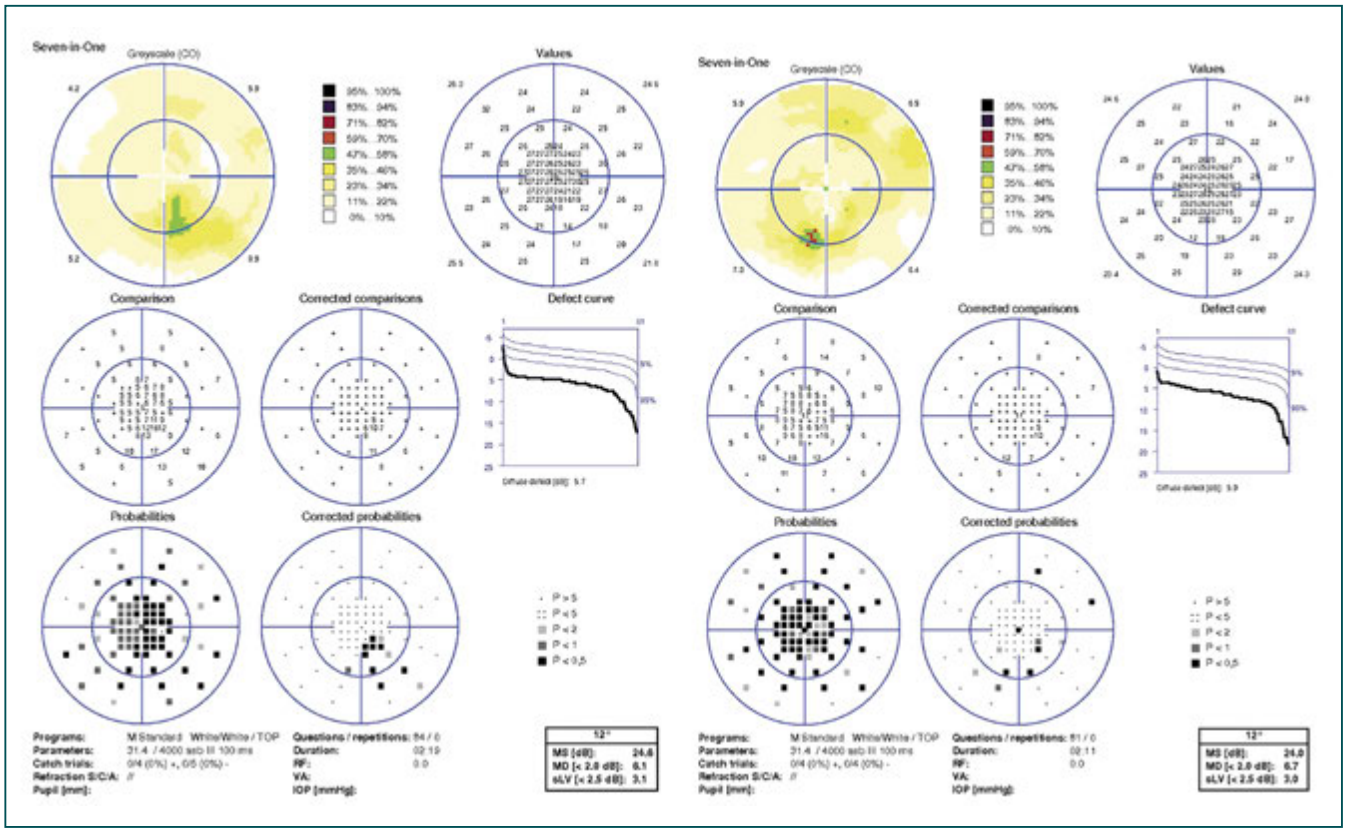

Figure 9: Case 3 – Octopus M-TOP visual fields of the left eye (left) and right eye (right).

tion was noted sub-foveally OU (**figure 4**, bottom). The normal FAF suggests a healthy RPE and the subtle OCT findings are consistent with his reduced central vision. The mfERG showed reduced outer retinal responses centrally (**figure 5**). This corresponded well with the moderate central decreased sensitivity displayed on the Octopus M-Top visual field OU (**figure 6**). Genetic testing and ffERG were performed by an outside provider, which confirmed a mutation in the *RP1L1* gene and displayed normal rod and cone function.

Case 3

65-year-old black male with a history of OCMD and glaucoma suspicion OU presented to the UEC for follow-up. The patient denied any changes in vision. He had a longstanding constant left exotropia and glaucoma suspicion secondary to large cup-to-disc ratio. His medical history was unremarkable, and he was not on any medications.

His BCVA was 20/200 OD/OS. External testing was unremarkable and anterior segment was positive for dry eye, arcus, and significant mixed cataracts OU. DFE displayed distinct optic nerve margins, large cupping (0.80 OD/0.85 OS) and intact neuroretinal rim. His vasculature was healthy appearing and normal caliber. His macula had mottling OU, worse in the left eye (**figure 7**, top), and peripheral retina was unremarkable on binocular indirect ophthalmoscopy.

The FAF displayed central hyper-AF OD and central hypo-AF with surrounding hyper-AF OS (**figure 7**, middle). Macular OCT had mild PIL attenuation and disruption OD and central outer retinal atrophy OS (**figure 7**, bottom). The central hyper-AF OD is consistent with stressed RPE cells underlying the macula. The central hypo-AF with surrounding hyper-AF OS is consistent outer retinal atrophy centrally, as seen on OCT, and stressed RPE cells surrounding the area of atrophy. His mfERG showed diffuse diminished amplitudes OU with some responses in the superior field of the right eye (**figure 8**) and his ffERG displayed normal cone and rod function. Octopus M-Top visual field revealed moderate superior paracentral depression OD and a moderate central scotoma with inferior depression OS (**figure 9**). The results of the mfERG and visual field correlate as they both display reduced responses centrally, worse in the left eye. Due to the larger field of view tested with the mfERG as compared to the visual field, the ERG shows more expansive depression than the visual field. Genetic testing and ffERG was performed by an outside provider that confirmed mutation in *RP1L1* gene and displayed normal rod and cone function.

Discussion

Occult macular dystrophy is generally associated with a mutation in the *RP1L1* gene and an autosomal dominant inheritance pattern, however, sporadic cases without this specific mutation have been documented.[1,7] Mutations in this gene have also been identified in other photoreceptor diseases such as retinitis pigmentosa.[2] The *RP1L1* gene is expressed

in both the inner and outer segments of the rod and cone photoreceptors and is suggested to play a role in the morphogenesis of photoreceptors, however, the exact function is not yet understood.[7]

Patients affected by occult macular dystrophy typically present with a progressive decline in visual acuity without visible fundus abnormalities. Fluorescein angiography and full field ERG testing will be normal, while multifocal or focal ERG and spectral domain-OCT (SD-OCT) will display abnormalities which correlate with the level of visual dysfunction.[13] As demonstrated in our case series and confirmed with genetic testing, there may be a wider range of phenotypic presentation of this condition than previously suggested.

Automated perimetry and electrophysiological testing are highly useful in confirming functional vision loss when the initial clinical exam is normal. Visual field testing will show central depression which correlates with a decline in visual acuity with preservation of peripheral vision. Electrophysiological testing, a more objective measurement of functional vision, demonstrates a progressive reduction in central outer retinal macular responses while non-central retinal function remains unaffected.[1,2] This peripheral retinal sparing results in a normal ffERG which assesses global retinal function, with an abnormal multifocal or focal ERG[1,2] which specifically assess macular function. Electrophysiological testing is highly sensitive for detection of this condition, especially early in the disease process, and can be useful in differentiating OCMD from other inherited retinal conditions such as Stargardt disease and other cone dystrophies which preferentially affect central vision.[7] In these conditions, the photopic response in ffERG testing will often be diminished while photopic responses are normal in OCMD despite confirmed central functional visual loss.

Functional testing such as automated perimetry and electrophysiological testing require patient cooperation and accurate fixation for extended periods of time. Although highly sensitive in the early stages of this disease,[7] patients with poor fixation associated with low vision can show variable results on mfERG and visual field testing which may preclude practitioners from accurately monitoring this condition for progression. Structural testing with less subjectivity such as SD-OCT, when used in combination with functional testing, can be highly useful in the detection of this disease. Furthermore, SD-OCT may be more useful in monitoring long-term disease progression.[7]

Patients with this condition display macular structural abnormalities on SD-OCT testing related to photoreceptor disruption which result in foveal thinning.[8,13] Macular photoreceptor thickness has been directly correlated with foveal amplitude on mfERG and threshold values on visual field testing,[8] indicating that these values correspond with levels of visual dysfunction and can provide useful quantifiable data to monitor this disease for structural and functional progression. Qualitative analysis of SD-OCT scans localizes structural abnormalities which contribute to this retinal thinning. These abnormalities are visible in the cone outer segment termination (COST) line and the inner segment/outer segment (IS/OS) line. Specifically, the COST line is absent in the macula and the IS/OS line is thickened and blurred in patients with this condition.[7] This localization of structural anomalies which correlate with functional vision loss confirms that pathophysiological changes related to the disease process in occult macular dystrophy occur at the level of the photoreceptors. Unlike other inherited retinal diseases which preferentially affect photoreceptors, the retinal pigment epithelium remains unaffected in most cases.[7]

Other structural testing such as fundus photography and fundus autofluorescence have proven to be less useful in occult macular dystrophy. Since fundus examination is typically normal, serial fundus photography is not beneficial in the detection or documentation of this condition. Fundus autofluorescence, often employed in addition to standard fundus photography, is often highly useful in the diagnosis and monitoring of most inherited retinal diseases, however, testing is normal or minimally abnormal in occult macular dystrophy. FAF detects the abnormal accumulation (hyper-AF) or absence (hypo-AF) of lipofuscin in the RPE. Since this structure remains intact throughout the course of this disease, findings will be normal or display very few abnormalities that are out of proportion to visual loss and results of other diagnostic tests.[8] Normal or near-normal FAF findings confirm that retinal dysfunction does not extend into the RPE and likely explains why fundus appearance is typically normal in these cases.[8]

It is still not fully understood why only macular function is affected and non-macular cones and the RPE remain relatively unaffected throughout the disease course, features that differ when compared to cone dystrophies.[7] Although the implication of *RP1L1* has been well documented in multiple IRDs, specific pathophysiology related to varying presentations of these diseases that would potentially explain this preferential effect is still unclear. More research is needed in these areas to lead to a better understanding of the pathophysiology of the disease which may lead to treatment options in the future.

Conclusion

Occult macular dystrophy is an uncommon autosomal-dominant disease associated with a mutation in the *RP1L1* gene. As the name suggests, this condition can pose a diagnostic challenge due to a normal funduscopic exam in the setting of reduced visual acuity. With the advent of SD-OCT, use of electrophysiological testing, and the increased accessibility of genetic testing, diagnosis of this condition no longer needs to be considered a diagnosis of exclusion. Furthermore, access to these diagnostic tests has likely resulted in more accurate and timely diagnosis of this hereditary condition as well as the identification of a wider range of clinical presentations. As our case study demonstrates, although individuals with this condition typically appear funduscopically normal, there may be a broader phenotypic spectrum of occult macular dystrophy than previously suspected.

Conflict of interests

The authors declare that there is no conflict of interests regarding the methods and devices mentioned in the article.

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