Retina Publish Ahead of Print
DOI: 10.1097/IAE.0000000000004223

Outer Retinal Columnar Abnormalities (ORCA): a novel optical coherence tomography sign of *CRB1* maculopathy?

Authors

Gabriela Grimaldi[1-2] MD, Moreno Menghini[1] MD, Omar Mahroo[2] PhD FRCOphth, Andrew Webster[2] MD FRCOphth, Michel Michaelides[2] MD FRCOphth, Claudia Liang Peng[2] BSc MBBS, Catherine Egan[2] FRANZCO, Adnan Tufail[2] MD FRCOphth

Departmental affiliation:

[1] Department of Ophthalmology, Institute of Clinical Neurosciences of Southern Switzerland (INSI), Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland.

[2] Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom; Institute of Ophthalmology, University College London, London, United Kingdom.

Financial disclosure

This study was supported by grants from the National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. All authors attest that they have no proprietary interest.

Corresponding author:

Dr Gabriela Grimaldi

Ophthalmology department, Ospedale Italiano, Via Pietro Capelli 1, 6962 Viganello, CH

Email address: gabriela.grimaldi@eoc.ch

Key words CRB1, macular dystrophy, OCT, optical coherence tomography, ORCA, outer retinal Columnar Abnormalities, retina, retinal dystrophy

Summary Statement Outer retinal columnar abnormalities (ORCA) are a novel optical coherence tomography sign of *CRB1*-related maculopathy.

Abstract

Purpose: To report a novel optical coherence tomography (OCT) sign in the context of *CRB1*-related maculopathy, termed outer retinal columnar abnormalities (ORCA).

Methods: Retrospective, multicenter observational case series of 14 eyes of 8 patients with molecularly confirmed *CRB1*-related maculopathy and ORCA. Multimodal

imaging scans and medical records patients with *CRB1*-related maculopathy were reviewed. Outcome measures included best-corrected visual acuity (BCVA), central subfield thickness on spectral-domain OCT (SD-OCT), presence of ORCAs and analysis of their change in appearance over time.

Results: At baseline, mean age was 18 +/- 10 years (range 9-36). All patients had an isolated macular dystrophy except for 1 case harboring a triallelic pathogenic variant. Variant c.498_506del was found in 9 cases (88%). At presentation, ORCA were visible on macular SD-OCT in all cases as multiform, vertical hyperreflective columnar alterations extending from the ellipsoid to the outer plexiform layer, with a variable degree of hyporeflective cystic spaces in the outer and inner nuclear layers. Over 6 +/- 4.7 follow-up years, the presence of ORCA varied greatly with a decrease in ORCA associated with sequential development of retinal atrophy.

Conclusions: A high suspicion for *CRB1*-associated retinal dystrophy should arise in the presence of ORCA on SD-OCT, prompting genetic testing.

Introduction

CRB1-associated retinopathy designates a range of inherited retinal diseases occurring due to biallelic pathogenic variants in the *CRB1* gene, a human homologue of the Drosophila melanogaster gene crumbs (crb). Clinical phenotypes vary widely, including Leber congenital amaurosis/early childhood onset severe retinal dystrophy, retinitis pigmentosa (RP), cone-rod dystrophy and isolated macular dystrophies. [1]

With the advent of optical coherence tomography (OCT), peculiar imaging features have been identified in patients with *CRB1* retinal dystrophies. Typical OCT findings are abnormal lamination with retinal thickening and disorganization of the retinal layers.[1,2] In a subgroup of patients, macular cystic changes represent the only detectable abnormality on fundus evaluation, posing a complex diagnostic challenge.[3,4,5(p1),6(p1)]

We describe a novel OCT feature, characterized by the presence of multifocal hyper-reflective columnar changes at the level of the outer retinal layers in the macula, which we have termed Outer Retinal Columnar Abnormalities (ORCA). We report the occurrence and natural history in the context of *CRB1*-related maculopathy, of which ORCA may represent a characteristic imaging feature, and hypothesize on its underlying pathophysiology.

Methods

This was a retrospective observational study including patients with molecularly confirmed *CRB1*-related maculopathy examined at the genetics outpatient clinic of two institutions (Ospedale Italiano, Ente Ospedaliero Cantonale, Lugano, Switzerland and Moorfields Eye Hospital NHS Foundation Trust, London, UK). The study protocol

adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committees of the participating institutions.

Electronic medical records of patients with *CRB1*-related maculopathy were reviewed and data collected included: demographic information, genetic mutation analysis, Snellen best corrected visual acuity (BCVA) at the time of presentation and at the last available follow-up and clinical examination findings. Cases with ORCA were identified through manual revision of macular OCT scans of all patients with *CRB1*-related maculopathy. Multimodal imaging was analyzed including color fundus photographs, near-infrared reflectance (NIR), spectral-domain OCT (SD-OCT), short-wavelength fundus autofluorescence and fluorescein angiography where available. Multimodal retinal imaging was acquired with the Heidelberg Spectralis® (Heidelberg Engineering, Heidelberg, Germany). Central subfield thickness (CST) measurements were obtained from serial eye-tracked volumetric OCT scans at the time of presentation and at the last available follow-up appointment.

Results

Fifteen eyes with ORCA from 8 patients with genetically confirmed *CRB1* maculopathy were included in the study. ORCA were noted in 15 out of 40 eyes with *CRB1* maculopathy (37.5%). Patients' demographic, clinical and imaging data are summarized in Table 1. Five patients were male (62%) and 3 were female (38%). The mean age at the time of presentation was 18 +/- 10 years (range 9-36 years) and the mean follow-up time was 6 +/- 4.7 years (range 1-15 years). There was no history of laser exposure in any case. No intraocular inflammatory signs were noted.

At baseline, mean BCVA was 20/32. On fundus assessment at presentation, extramacular abnormalities were observed only in 1 case (proband 7), whereas the remaining patients all presented with isolated maculopathy (87.5%). The most prevalent allele pathogenic variant identified was c.498_506del (7 probands, 88%).

Macular SD-OCT at the time of presentation showed macular cystic changes in all cases. Baseline CST measured 374 +/- 99 µm (range 172-535 µm). ORCA were present in all eyes at presentation, appearing on SD-OCT as vertical hyperreflective columnar alterations extending from the ellipsoid layer variably up to the outer plexiform layer (OPL). In some cases, a peculiar centrifugal curvature towards the OPL could be detected. Possible locations for ORCA included the fovea (central 1 mm) and surrounding parafovea (3 mm ring quadrants) and perifovea (5 mm ring quadrants) over 360 degrees. Overall, configuration, density and distribution of ORCA was quite variable between study eyes and within the same eye at different time points (Figure 1). ORCA were observed bilaterally in 7 out of 8 patients (87.5%). In the remaining two cases of unilateral ORCA, the fellow eye showed diffuse outer foveal atrophy. In bilateral cases, an asymmetry in macular thickening (CST difference >100 um between eyes) was noted in 2 cases (28%). No corresponding abnormality was noted on NIR, autofluorescence and fluorescein angiography. In particular, fluorescein angiograms were obtained for 2 patients where absence of leakage was highlighted. No additional macular abnormality was observed on multimodal imaging in all cases.

At the last follow-up visit, mean CST was 243 +/- 85 µm. A decrease in CST was noted in 13 eyes (86%), with a mean thickness reduction of 156 +/- 93 µm. In the remaining 2 eyes, worsening of macular cystic spaces was observed with a mean thickness increase of 33 µm (range 7-59 µm). Final mean BCVA was 20/32, with visual improvement being recorded in 6 eyes (40%). Visual acuity remained stable in 2 eyes, whereas 7 eyes

had a final worse BCVA compared to baseline (46%). ORCA were observed at final follow-up in 12 eyes (80%). Differences in the evolution of ORCA on OCT imaging over time are shown in Figure 2. ORCA decreased in 2 eyes (13%) and completely disappeared in 4 eyes (26%), along with the development of outer retinal atrophy in all cases. An increase in the number of ORCA was noted in 2 eyes (13%), while ORCA remained overall stable in 7 eyes (46%).

Discussion

To the best of our knowledge, our study is the largest case series describing the occurrence and natural history of ORCA in *CRB1*-maculopathy.

In the current series, ORCA were highlighted on macular SD-OCT in all study eyes at the time of presentation, undergoing variable changes over time. The presence of ORCA was associated with a variable degree of visual impairment, although it is currently unclear if ORCA only represent a subclinical structural alteration or if vision might be affected by their presence and to what extend this may occur. The site of these abnormalities, at the level of the outer hyper-reflective retinal layers, as shown on structural OCT scans, does not seem accidental. It is well known that the *CRB1* gene plays a major role in photoreceptor morphogenesis and retinal development, as well as enabling apical-basal polarity and cell adhesion in the retinal neuroepithelium.[7–9] Specifically, the transmembrane *CRB1* protein is located at the level of the subapical region of Müller and photoreceptor cells, regulating maintenance of zonula adherens junctions between Müller cells, photoreceptors, and the external limiting membrane, which represents an important morphological landmark on macular OCT. The complexity of *CRB1* roles explains the multitude of phenotypes reported in patients

with genetically confirmed *CRB1*-related retinal dystrophy, spanning from early childhood onset severe retinal dystrophy to milder clinical forms limited to the macular region.[10] In our case series, isolated maculopathy was by far the most frequent clinical phenotype identified, seemingly driven by the common allelic genetic variant c.498_506del, which was found in the majority of cases. In this context, ORCA may represent the mild end of a spectrum of OCT abnormalities typical of *CRB1*-related retinopathy, notably appearing in combination with cystic spaces. The fact that proband 7 had more widespread retinal degeneration, extending beyond the posterior pole, might be related with the finding of three pathogenic allelic variants, possibly explaining the more severe phenotype. When compared with subgroups with and without maculopathy from large published series, our data mirrors the more favorable phenotype demonstrated for patients with *CRB1*-maculopathy versus patients without maculopathy.[1,5] Whether ORCA might be a prodromic sign of or contributing factor for the presence of cystic spaces on OCT in case of mutated *CRB1* is still to be understood, although their presence might signal a specific stage of retinal degeneration. The fact that ORCA seem to markedly decrease or disappear with resolution of cystic spaces over time would suggest that these two features might be strongly intertwined. It is unclear why some patients develop outer retinal atrophy while others maintain relatively good vision in the context of persistent ORCA, despite a similar clinical picture at presentation with coexistence of ORCA and cystic spaces. The ocular asymmetry in proband 7 (atrophy in the fellow eye) may be explained by different stages in the disease progression.

ORCA were first reported as an imaging feature by our group in a case of a 18-year-old female patient with dense deposit disease (DDD, also known as membranoproliferative glomerulonephritis type II), alongside drusen and cystoid macular edema.[11] Although

ORCA may represent an exceptional feature of DDD, the possibility of dual pathology with an underlying CBR1-related retinal dystrophy cannot be excluded.

Interestingly, a striking resemblance can be observed on OCT between ORCA and retinal lesions reported in association with handheld laser-induced maculopathy.[12–14] A few case reports from the literature consistently show foveal disruption of the ellipsoid zone and external limiting membrane from vertically-oriented hyper-reflective streaks extending to the OPL. Studies on animal models of laser-induced maculopathy revealed migration of microglial cells to the site of photoreceptor injury, matching increased scattering throughout the outer retinal layers on simultaneous high-resolution OCT, followed by tissue remodeling and spontaneous resolution.[15,16] Although parallel glia-mediated macular changes would represent a plausible explanation of ORCA, it should be noted that corresponding autofluorescence and fundus abnormalities were always observed in laser-induced maculopathy cases, characterized by hypopigmented and hypofluorescent macular streaks respectively, that were not noted if this *CRB1* cohort.[12]. Further no history of laser exposure was present in our case series. We hypothesize that the similar outer retinal columnar lesions in laser and our *CRB1* cohort represent a common cellular pathology that remains to be explored.

It should be noted that the OCT feature identified in this study might not be wholly specific for *CRB1*-maculopathy. In addition to laser-associated retinopathy, similar changes have been occasionally observed in other maculopathies, sometimes in association with outer retinal deposits. However, the prevalence appears high in *CRB1*-maculopathy cases and there appear to be subtle differences compared with other maculopathies. Hyperreflective outer retinal abnormalities have been identified in patients and carriers of *LAMP2* pathogenic variants (associated with Danon disease), and these show some similarities to the features described in the present study.[17,18]

However, in the *LAMP2* cases, the underlying ellipsoid zone (EZ) line appears intact, whilst the ORCA feature identified in the present study is associated with an underlying focal defect in the EZ line, more than would be expected simply from optical shadowing.

Our hypothesis is that ORCA might indeed represent a characteristic sign of *CRB1*-maculopathy, whose identification on OCT should prompt further genetic analyses to rule out an underlying *CRB1*-associated retinal dystrophy. This hypothesis seems substantiated by the observation that ORCA can be identified on the OCT figures from published reports on *CRB1*-maculopathy, constituting a consistent and unifying OCT feature among different case series.[1,3,6,19–22] Recently, similar OCT findings were also observed in a case series of 2 patients with confirmed *CRB1*-maculopathy[23], further reinforcing the potential diagnostic value of ORCA in relation with *CRB1*-maculopathy.

In conclusion, we report of a novel OCT feature of *CRB1*-maculopathy termed ORCA. The utility of ORCA as an aid for differential diagnosis of *CRB1*-associated dystrophies is particularly relevant considering cystoid macular edema is a non-specific feature which may pose a significant diagnostic challenge when encountered in otherwise healthy patients of young age, and as such might aid to avoid unnecessary investigations and interventions. Further studies with longer follow-up are warranted to better understand the significance of ORCA from a morpho-functional perspective in patients with *CRB1*-maculopathy and to explore ORCA signs in other retinal disease to identify common cellular or genetic pathogenic mechanisms.

References

1. Daich Varela M, Georgiou M, Alswaiti Y, et al. CRB1-Associated Retinal Dystrophies: Genetics, Clinical Characteristics, and Natural History. *Am J Ophthalmol*. 2023;246:107-121. doi:10.1016/j.ajo.2022.09.002

2. Jacobson SG. Crumbs homolog 1 (CRB1) mutations result in a thick human retina with abnormal lamination. *Hum Mol Genet*. 2003;12(9):1073-1078. doi:10.1093/hmg/ddg117

3. Oh DJ, Daily MJ, Grassi MA. CRB1 maculopathy presenting as fenestrated sheen macular dystrophy with 15-year follow-up. *Doc Ophthalmol*. 2021;142(3):381-388. doi:10.1007/s10633-020-09810-y

4. Khan AO, Aldahmesh MA, Abu-Safieh L, Alkuraya FS. Childhood Cone-rod Dystrophy with Macular Cystic Degeneration from Recessive *CRB1* Mutation. *Ophthalmic Genet*. 2014;35(3):130-137. doi:10.3109/13816810.2013.804097

5. Talib M, van Schooneveld MJ, van Genderen MM, et al. Genotypic and Phenotypic Characteristics of CRB1 -Associated Retinal Dystrophies. *Ophthalmology*. 2017;124(6):884-895. doi:10.1016/j.ophtha.2017.01.047

6. Vincent A, Ng J, Gerth-Kahlert C, et al. Biallelic Mutations in *CRB1* Underlie Autosomal Recessive Familial Foveal Retinoschisis. *Investig Opthalmology Vis Sci*. 2016;57(6):2637. doi:10.1167/iovs.15-18281

7. Richard M, Roepman R, Aartsen WM, et al. Towards understanding CRUMBS function in retinal dystrophies. *Hum Mol Genet*. 2006;15(suppl_2):R235-R243. doi:10.1093/hmg/ddl195

8. Pellikka M, Tanentzapf G, Pinto M, et al. Crumbs, the Drosophila homologue of human CRB1/RP12, is essential for photoreceptor morphogenesis. *Nature*. 2002;416(6877):143-149. doi:10.1038/nature721

9. Alves CH, Pellissier LP, Wijnholds J. The CRB1 and adherens junction complex proteins in retinal development and maintenance. *Prog Retin Eye Res*. 2014;40:35-52. doi:10.1016/j.preteyeres.2014.01.001

10. Ehrenberg M, Pierce EA, Cox GF, Fulton AB. *CRB1* : One Gene, Many Phenotypes. *Semin Ophthalmol*. 2013;28(5-6):397-405. doi:10.3109/08820538.2013.825277

11. Peng CL, Olvera-Barrios A, Schwartz R et al. Novel Outer Retinal Columnar Abnormalities (ORCA) and Non-Vasogenic Cystoid Macular Edema in Dense Deposit Disease. *Retin Cases Brief Rep*. 2023 Oct 16. doi: 10.1097/ICB.0000000000001488

12. Bhavsar KV, Wilson D, Margolis R, et al. Multimodal Imaging in Handheld Laser-Induced Maculopathy. *Am J Ophthalmol*. 2015;159(2):227-231.e2. doi:10.1016/j.ajo.2014.10.020

13. Jiang F, Shi Y, Wang Z, Yang X. Case series of photic maculopathy associated with exposure to a plasma flash induced by a femtosecond laser. *Lasers Surg Med*. 2022;54(5):631-638. doi:10.1002/lsm.23519

14. Rusu I, Sherman J, Gallego-Pinazo R, Lam M, Freund KB. SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY AND FUNDUS AUTOFLUORESCENCE FINDINGS IN A CASE OF LASER POINTER–INDUCED MACULOPATHY. *Retin Cases Brief Rep*. 2013;Publish Ahead of Print. doi:10.1097/ICB.0b013e3182965291

15. Belokopytov M, Belkin M, Dubinsky G, Epstein Y, Rosner M. DEVELOPMENT AND RECOVERY OF LASER-INDUCED RETINAL LESION IN RATS. *Retina*. 2010;30(4):662-670. doi:10.1097/IAE.0b013e3181bd2fa9

16. Miller EB, Zhang P, Ching K, Pugh EN, Burns ME. In vivo imaging reveals transient microglia recruitment and functional recovery of photoreceptor signaling after injury. *Proc Natl Acad Sci*. 2019;116(33):16603-16612. doi:10.1073/pnas.1903336116

17. Kousal B, Majer F, Vlaskova H, et al. Pigmentary retinopathy can indicate the presence of pathogenic *LAMP2* variants even in somatic mosaic carriers with no additional signs of Danon disease. *Acta Ophthalmol (Copenh)*. 2021;99(1):61-68. doi:10.1111/aos.14478

18. Hasegawa A, Noda K, Fujiya A et al. Outer Retinal Abnormalities in a Patient with Danon Disease. *Retin Cases Brief Rep*. 2022;16(5):619-621. doi:10.1097/ICB.0000000000001043

19. Wolfson Y, Applegate CD, Strauss RW, Han IC, Scholl HP. *CRB1* -Related Maculopathy With Cystoid Macular Edema. *JAMA Ophthalmol*. 2015;133(11):1357. doi:10.1001/jamaophthalmol.2015.2814

20. UK Inherited Retinal Disease Consortium, Khan KN, Robson A, et al. A clinical and molecular characterisation of CRB1-associated maculopathy. *Eur J Hum Genet*. 2018;26(5):687-694. doi:10.1038/s41431-017-0082-2

21. Oh DJ, Sheth V, Fishman GA, Grassi MA. Simplex Crumbs Homologue 1 Maculopathy Masquerading as Juvenile X-Linked Retinoschisis in Male Patients. *J Vitreoretin Dis*. 2020;4(5):437-440. doi:10.1177/2474126420916079

22. Roshandel D, Thompson JA, Heath Jeffery RC, et al. Multimodal Retinal Imaging and Microperimetry Reveal a Novel Phenotype and Potential Trial End Points in *CRB1* -Associated Retinopathies. *Transl Vis Sci Technol*. 2021;10(2):38. doi:10.1167/tvst.10.2.38

23. Bellingrath JS, Birtel J, Yusuf IH et al. Optical Coherence Tomography Feature of Retinoschisis in CRB1-Associated Maculopathy. *JAMA Ophthalmol*. 2024;142(2):158-161. doi:10.1001/jamaophthalmol.2023.5886

Figure legends

Figure 1. *Evolution of bilateral outer retinal columnar abnormalities (ORCA, arrowheads) on optical coherence tomography (OCT) in proband 5.* **A-B.** At presentation, mild retinal thickening is seen in the right eye, where multiform ORCA can be detected centrally and perifoveally (A). Isolated ORCA can be observed temporally to the fovea in the left eye (B). **C-D.** At 1-year follow-up, central cystic spaces and microcystoid edema appear in the right eye with further subfoveal thickening, while new ORCA appear temporally and nasally. In the left eye, new ORCA appear centrally and nasally, with incipient cystic changes at the inner nuclear layer. **E-F.** At 2-year follow-up, cystic spaces appear slightly increased in the right, with disappearance of previous ORCA and onset of new ORCA temporally (E). In the left eye, central ORCA increase in number and elongation, curving inwardly across the outer nuclear layer, with changes in eccentric ORCA distribution (F).

Figure 2. *Longitudinal changes in outer retinal columnar abnormalities (ORCA) on optical coherence tomography (OCT).* **A-B. Proband 1.** Macular OCT of the right eye at presentation shows central cystic spaces and focal ORCA (arrowheads) (A). Fifteen years later, cystic spaces had completely resolved with good preservation of outer retinal layers and only faintly visible ORCA (arrowheads). (B). **C-D. Proband 2.** Macular OCT of the right eye at presentation reveals severe cystoid spaces with focal eccentric ORCA (arrowheads) (C). At 9 years of follow-up, cystic spaces have markedly improved but is replaced by outer retinal loss with no visible ORCA (D). **E-F. Proband 6.** Macular OCT of the left eye at presentation reveals cystoid spaces with central outer retinal disruption and multifocal eccentric ORCA (arrowheads) (C). One year later, following 6-month treatment with topical dorzolamide, a decrease in cystoid

spaces is observed with partial, subfoveal restoration of the outer retinal layers and changes in shape and distribution of ORCA (arrowheads) (D).

Patients' demographics, clinical and imaging features

N	Age at presentation (years)	Gender	Affected eye	Clinical Phenotype	Allele 1 (Amino acid change; mutation type)	Allele 2 (Amino acid change; mutation type)	Snellen BCVA at presentation (CST in um)		FUP (years)	Final Snellen BCVA (CST in um)		Clinical course
							Right Eye	Left Eye		Right Eye	Left Eye	
MEH 1	13	M	BE	Isolated maculopathy	c.498_506del (p.Ile167_Gly169del; in-frame)	c.2688T>A (p.Cys896Ter; nonsense)	20/15 (376)	20/80 (324)	15	20/20 (238)	20/20 (235)	Cystic changes resolution, scant ORCA
MEH 2	8	F	BE	Isolated maculopathy	c.498_506del (p.Ile167_Gly169del; in-frame)	c.2688T>A (p.Cys896Ter; nonsense)	20/25 (535)	20/30 (465)	9	20/60 (202)	20/60 (147)	Cystic changes + ORCA resolution, outer retinal atrophy
MEH 3	20	M	BE	Isolated maculopathy	c.498_506del (p.Ile167_Gly169del; in-frame)	c3827_3828del (p.Glu1276Valfs*4; frameshift)	20/40 (379)	20/30 (239)	8	20/60 (185)	20/25 (147)	Persistent cystic spaces + ORCA
MEH 4	10	M	BE	Isolated maculopathy	c.498_506del (p.Ile167_Gly169del; in-frame)	c.2308G>T (p.Gly770Cys; missense)	20/30 (425)	20/30 (428)	6	20/25 (216)	20/25 (230)	Cystic spaces resolution, scant ORCA
MEH 5	21	F	BE	Isolated maculopathy	c2839G>A (p.Glu947Lys;	c.3307G>A (p.Gly1103Arg;	20/40 (295)	20/15 (304)	2	20/60 (354)	20/15 (311)	Cystic spaces + ORCA increase

					in-frame)	missense)						
EOC 6	36	M	BE	Isolated maculopathy	c.498_506del (p.Ile167_Gly169del; in-frame)	c.522T>A (p.Cys174Ter; nonsense)	20/30 (427)	20/40 (489)	1	20/25 (297)	20/30 (426)	Cystic spaces resolution, persistent ORCA
MEH 7	31	M	LE	Retinal dystrophy with macular involvement	c.498_506del (p.Ile167_Gly169del; in-frame)	c.4142C>G (p.Pro1381Arg; in-frame) c.3625G>A (p.Val1209Met; missense)	20/120 (173)	20/20 (451)	7	20/120 (183)	20/30 (343)	Cystic spaces decrease, persistent ORCA
MEH 8	9	F	BE	Isolated maculopathy	c.498_506del (p.Ile167_Gly169del; in-frame)	c.2843G>A (p.Cys948Tyr; missense)	20/40 (172)	20/40 (305)	1	20/50 (157)	20/40 (164)	Cystic spaces + ORCA resolution, outer retinal atrophy

BCVA: Best corrected visual acuity; BE: Bilateral; CME: Cystoid macular edema; CST: Central subfield thickness FUP: Follow-up; LE: Left eye; ORCA: Outer Retinal Columnar Abnormalities;