



Rare occult macular dystrophy with a pathogenic variant in the RP1L1 gene in a patient of Swiss descent

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ABSTRACT

Purpose: We report a first case of bilateral occult macular dystrophy (OMD) with a c.133C>T (p.Arg45Trp) pathogenic variant in the retinitis pigmentosa 1-like 1 (*RP1L1*) gene in a patient of Caucasian Swiss descent.

Observations: A 34-year-old man presented with decreased visual acuity known since childhood. Fundus examination of both eyes revealed no pathology other than mildly increased granularity of the foveal retinal pigment epithelium. The full-field electroretinogram (ffERG) presented with normal findings while the multifocal electroretinogram (mfERG) showed severely reduced amplitudes of the foveal response. Optical coherence tomography (OCT) showed foveal outer retinal atrophy. Fundus autofluorescence (FAF) imaging demonstrated near-normal findings with minimal mottling at the posterior pole. The genetic analysis revealed a heterozygous pathogenic variant (c.133C>T, p.Arg45Trp) in the *RP1L1* gene.

Conclusion and importance: Our present case suggests that OMD shows a wide range of clinical presentations with a variety of ophthalmological findings, age of disease onset, visual acuity, and genetic diversity.

1. Introduction

Occult macular dystrophy (OMD) is an inherited retinal disease (IRD) marked by a progressive loss of central vision with preserved paracentral and peripheral retinal function.^{1,2} It is mostly inherited in an autosomal dominant manner and is caused by a pathogenic variant in the *RP1L1* gene with incomplete penetrance.³ To date, it has been assumed that these pathogenic variants are mostly predominant in patients of East Asian heritage.^{3,4} However, with the implementation of new generation sequencing (NGS) into daily clinical practice of IRDs these rare pathogenic variants are more likely to be found also within other ethnical groups.⁵ Here, we present a case of OMD caused by a Arg45Trp pathogenic gene variant described in a 34-year-old Caucasian patient of Swiss descent.^{3,4}

2. Case report

A 34-year-old gentleman was referred to our department with suspected central cone dystrophy, where he reported about visual acuity

deterioration since childhood. Best-corrected visual acuity measured under standardized Early Treatment Diabetic Retinopathy Study (ETDRS) conditions⁶ was 20/125 (ETDRS letter score: 45) and 20/160 (ETDRS letter score: 40) in his right and left eye, respectively. Intraocular pressure was normal with a normal anterior segment. Fundus examination of both eyes revealed minimal changes in the foveal retinal pigment epithelium (RPE). The full-field electroretinogram (ffERG, Diagnosys, LCC Espion system; ISCEV standard⁷) presented with normal findings of the scotopic, photopic and 30Hz flicker responses (Fig. 1). However, the multifocal electroretinogram (mfERG, Diagnosys, LCC Espion system; ISCEV standard⁸) presented with severely reduced amplitudes of the foveal response with preserved parafoveal signals (Fig. 2). Optical coherence tomography (OCT, Heidelberg Engineering Spectralis®) imaging showed a slightly discontinued ellipsoid zone line and foveal outer nuclear layer thinning (Fig. 3). Fundus autofluorescence (FAF) imaging demonstrated almost normal findings with minimal mottling of the posterior pole (Fig. 3). Kinetic visual field testing (V4e, III4e, I4e, III3e isopters tested with Octopus 900®, Haag-Streit AG Bern, Switzerland) revealed normal outer borders

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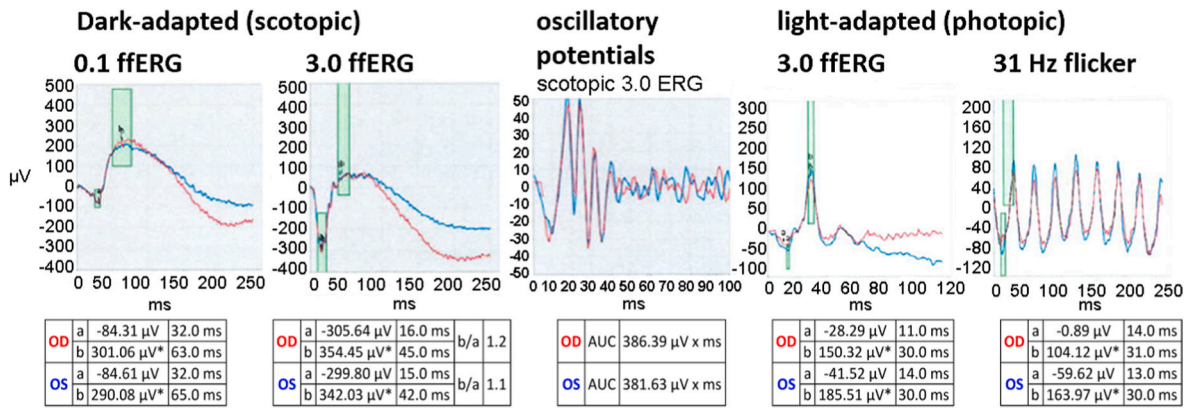


Fig. 1. Full-field electroretinogram (ffERG) on both eyes: dark-adapted (scotopic) 0.01 ERG presents normal rod-driven response on bipolar cells (b-wave); dark-adapted 3.0 ERG showing combined responses arising from photoreceptors (a-wave) and bipolar cells of both the rod and cone systems within normal limits; normal oscillatory potentials showing three main positive peaks followed by four smaller one; light-adapted (photopic) 3.0 ERG demonstrates regular single flash cone response as well as the activity of the cone system as seen in the 31Hz flicker ERG. The green boxes indicate normal values for implicit time and amplitude of age-matched controls. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

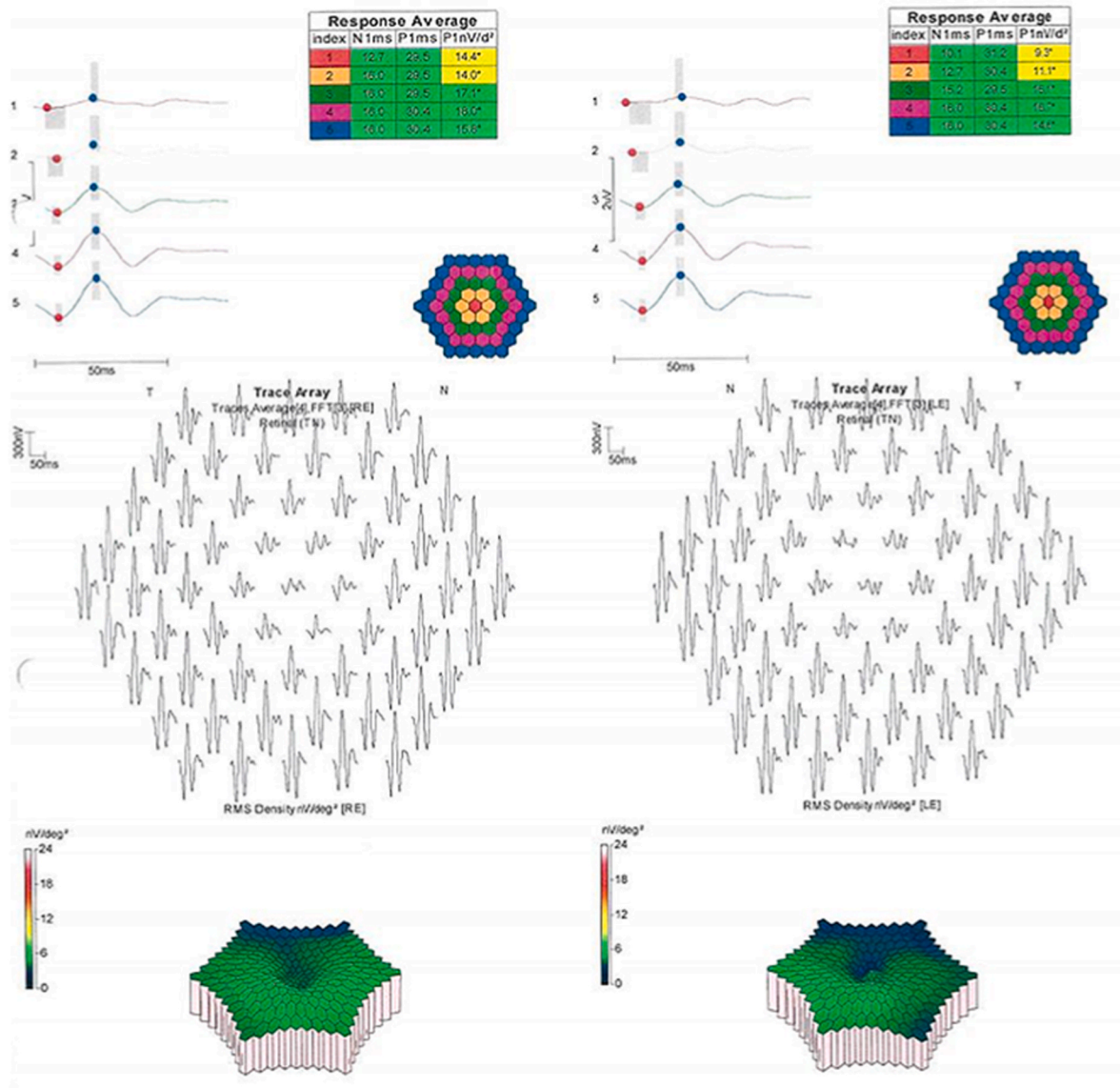


Fig. 2. Multifocal electroretinogram (mfERG) presenting with a lower amplitude of the foveal response with preserved parafoveal signals.

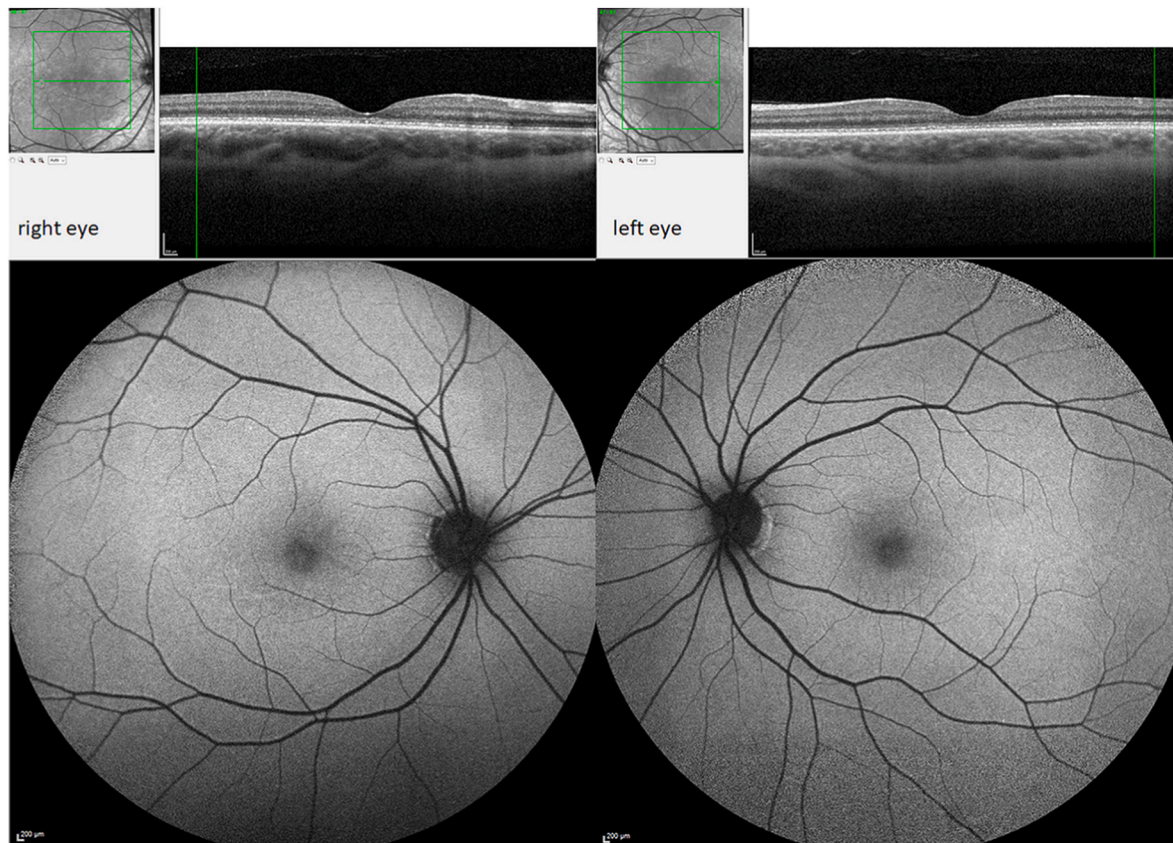


Fig. 3. Optical coherence tomography (OCT; top) showing disruptions of the ellipsoid zone line on both eyes. Fundus autofluorescence (FAF) imaging (bottom) demonstrates near-normal findings with minimal mottling at the posterior pole on both eyes.

(Fig. 4). A more detailed examination with microperimetry (Nidek, MP-3, Nidek Co, Japan, 10-2 pattern) revealed stable central fixation (shown in Fig. 4), however, with a diminished sensitivity of the foveal region while other retinal regions showed a normal sensitivity.

Molecular genetic testing with next-generation sequencing (whole exome sequencing, WES; Ophthalmogenetics, Department of Ophthalmology, University Hospital Bern) and pedigree analysis detected a heterozygous pathogenic variant in the *RP11* gene (c.133C>T; p. Arg45Trp).^{3,4} Taking all clinical findings into account we diagnosed OMD. Our patient had no Asian ancestors, also no consanguinity was known in the family. In agreement with the incomplete penetrance in OMD,⁹ the patient presents with a positive family history with similar symptoms of his sister who was not genetically tested yet but unaffected parents (Fig. 5).

3. Discussion

First described by Y. Miyake in 1989, OMD is characterized by central cone dysfunction and in some cases with rod dysfunction, resulting in a deterioration of the visual acuity despite having a nearly normal ophthalmoscopic appearance, normal fluorescein angiography, and normal ffERG^{1,2,10,11} The average age of symptom onset is 25–30 years, with a range from 2 to 74 years.^{5,9,12} Brockhurst and Sandberg¹¹ reported about four out of eight OMD patients with age of onset over 65 years, similar findings could be observed in previous cases.

So far, for OMD patients there is no evidence-based therapeutic option available. The rarity of the disease and the unknown function of the *RP11* gene are two major difficulties in developing a gene therapy for OMD. However, unlike many other IRDs, patients with OMD often do not become symptomatic until adulthood. Also, OMD seems to present with a slow and predictable disease progression. Therefore, OMD

appears to offer a large window of opportunities for therapeutic intervention and thus could become an interesting target for gene therapy in the future.

So far, pathogenic variants in *RP11* gene were likely to be found predominantly in people of East Asian descent.⁴ To the best of our knowledge, this is the first published case of a molecular genetically confirmed OMD case with a pathogenic variant in the *RP11* gene in Switzerland. This postulates how rare, diverse and often unrecognized this disease is in daily clinical practice. Physicians should consider OMD as a differential diagnosis of other retinal degenerations in patients with normal-appearing fundus and otherwise unexplained deterioration of visual acuity. An accurate investigation performed by ophthalmologists specialized in IRDs and the collaboration with an experienced laboratory for molecular genetics of the retina allows to establish the diagnosis of OMD.

Patient consent

Written informed consent was obtained from patient for publication of this case report and any accompanying images.

Financial disclosure statement

Dr. Scholl is member of the Scientific Advisory Board of: Apellis Switzerland GmbH, ARCTOS medical AG; Astellas Pharma Global Development, Inc./Astellas Institute for Regenerative Medicine; Biogen MA Inc.; Boehringer Ingelheim Pharma GmbH & Co; Gyroscope Therapeutics Ltd.; Janssen Research & Development, LLC (Johnson & Johnson); Novartis Pharma AG (CORE); Okuvision GmbH; Pharma Research & Early Development (pRED) of F. Hoffmann-La Roche Ltd; ReVision Therapeutics, Inc.; and Stargazer Pharmaceuticals, Inc. Dr. Scholl is paid

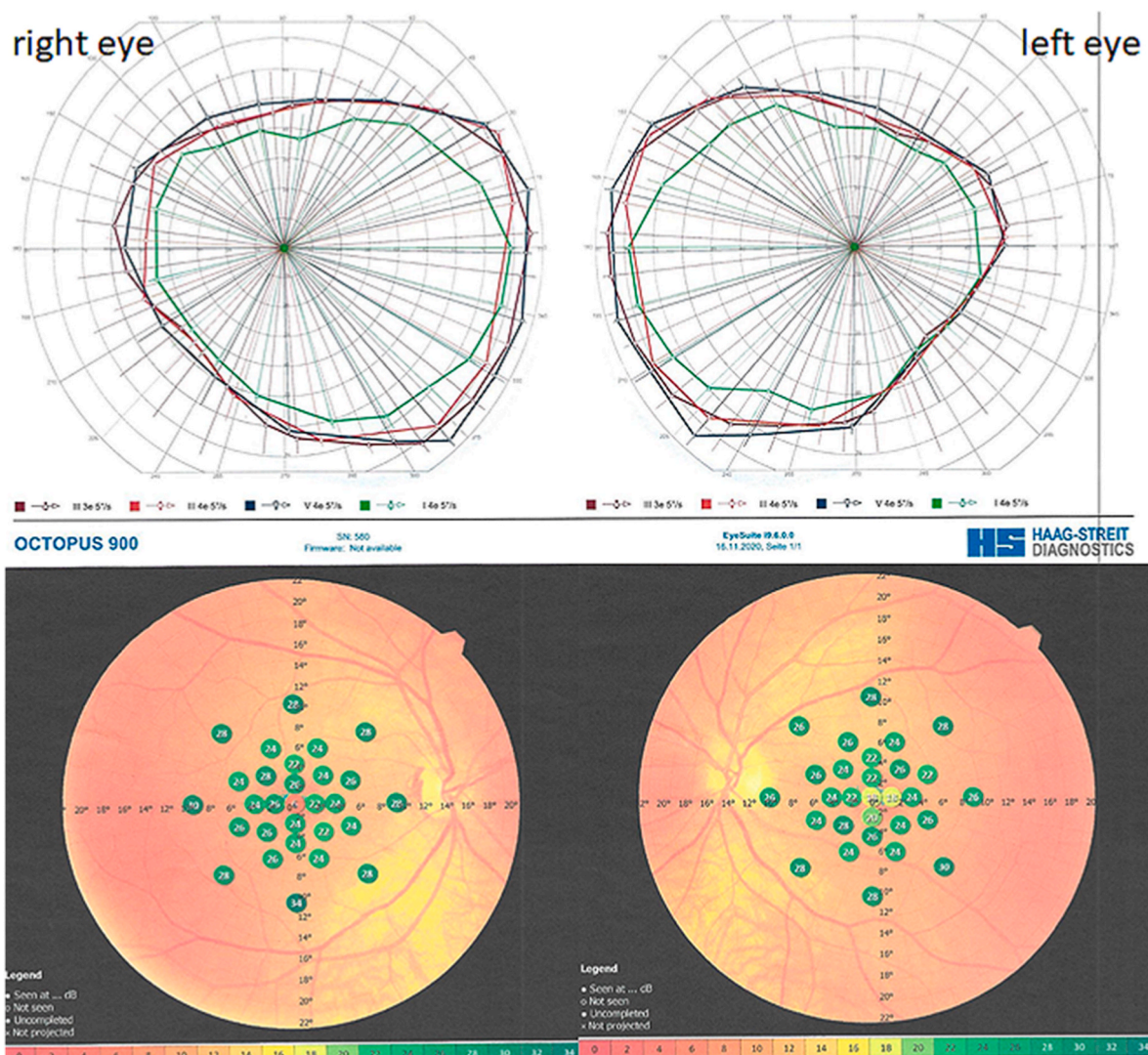


Fig. 4. Kinetic visual field testing (V4e, III4e, I4e, III3e isopters tested with Octopus 900®, Haag-Streit AG Bern, Switzerland; top) revealed normal outer borders. A more detailed examination with microperimetry (Nidek, MP-3, Nidek Co, Japan, 10-2 pattern; bottom) revealed stable central fixation, however, with a diminished sensitivity of the foveal region while the other retinal regions showed a normal sensitivity.

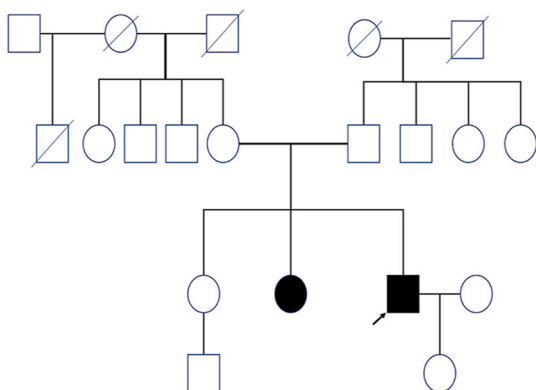


Fig. 5. The patient’s pedigree suggests an autosomal-dominant mode of inheritance with incomplete penetrance (black arrow: proband; colored black: affected phenotype, but not genetically tested yet).

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

All other authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing

arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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References

1. Miyake Y, Ichikawa K, Shiose Y, Kawase Y. Hereditary macular dystrophy without visible fundus abnormality. *Am J Ophthalmol.* 1989;108:292–299.
2. Miyake Y, Horiguchi M, Tomita N, Kondo M, Tanikawa A. Occult macular dystrophy. *Am J Ophthalmol.* 1996;122:644–653.
3. Akahori M, Tsunoda K, Miyake Y, Fukuda Y, Ishiura H. Dominant mutations in RP11L1 are responsible for occult macular dystrophy. *Am J Hum Genet.* 2010;87, 429–9.
4. Fujinami K, Yang L, Joo K, Tsunoda K, Kameya S. Clinical and genetic characteristics of East Asian patients with occult macular dystrophy (Miyake disease): East Asia occult macular dystrophy studies report number 1. *Ophthalmology.* 2019;126: 1432–1444.
5. Zobor D, Zobor G, Hipp S, Baumann B, Weisschuh N. Phenotype variations caused by mutations in the RP11L1 gene in a large mainly German cohort. *Invest Ophthalmol Vis Sci.* 2018;59:3041–3052.
6. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. *Ophthalmology.* 1991;98:741–756.
7. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE. ISCEV Standard for full-field clinical electroretinography (2015 update). *Doc Ophthalmol.* 2015;130: 1–12.
8. Hoffmann MB, Bach M, Kondo M, et al. ISCEV standard for clinical multifocal electroretinography (mfERG) (2021 update). *Doc Ophthalmol.* 2021;142:5–16.
9. Tsunoda K, Usui T, Hatase T, Yamai H, Fujinami K. Clinical characteristics of occult macular dystrophy in family with mutation of RP11L1 gene. *Retina-J Retinal Vitreous Dis.* 2012;32:1135–1147.
10. Wildberger H, Niemeyer G, Junghardt A. Multifocal electroretinogram (mfERG) in a family with occult macular dystrophy (OMD). *Klin Monatsbl Augenheilkd.* 2003;220: 111–115.
11. Brockhurst RJ, Sandberg MA. Optical coherence tomography findings in occult macular dystrophy. *Am J Ophthalmol.* 2007;143:516–518.
12. Nakamura N, Tsunoda K, Mizuno Y, Usui T, Hatase T. Clinical stages of occult macular dystrophy based on optical coherence tomographic findings. *Invest Ophthalmol Vis Sci.* 2019;60:4691–4700.