Jpn J Ophthalmol (2015) 59:71–80
DOI 10.1007/s10384-015-0371-7

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

REVIEW

Occult macular dystrophy

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Received: 5 December 2014 / Accepted: 15 December 2014 / Published online: 10 February 2015

Abstract Occult macular dystrophy (OMD) was first reported in 1989 as a hereditary macular disease without visible fundus abnormalities. Patients with OMD are characterized by a progressive decrease of visual acuity but have normal fundus and fluorescein angiograms with both the rod and cone components of the full-field electroretinograms (ERGs) essentially normal. However, the focal macular ERGs and multifocal ERGs are severely attenuated. These findings indicate that the retinal dysfunction is confined to the macula. Optical coherence tomography (OCT) has shown structural changes in the outer nuclear and/or photoreceptor layers. Genetic analyses of OMD pedigrees have identified dominant mutations in the *RP1L1* gene. However, the same mutations were not detected in sporadic cases, suggesting that several independent mutations can lead to the OMD phenotype. The purpose of this paper is to review the history of OMD, the visual functions determined psychophysically, ERG findings, OCT characteristics and genetic findings in patients with OMD.

Keywords Occult macular dystrophy · Focal macular ERG · Multifocal ERG · Optical coherence tomography · *RP1L1* gene

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Introduction

At the beginning of the 20th century, three well-known retinal diseases were identified by Japanese ophthalmologists, i.e., Oguchi disease [1], Takayasu disease [2] and Harada disease [3]. Each of these diseases has unique fundus findings, and their discoveries coincided with the development of new fundus examination techniques.

There are several hereditary retinal diseases in which fundus findings are normal and provide little information for diagnosis. In these diseases, the characteristics of the electroretinograms (ERGs) play an important role in the diagnosis. For example, congenital stationary night blindness (CSNB) with normal fundus findings is classified into complete and incomplete types by a detailed analysis of the full-field ERGs [4]. Although there were questions as to whether these two types of CSNB were different clinical entities, genetic analyses proved that the complete and incomplete types of CSNB were indeed different clinical entities [5–9]. Eyes with the cone dysfunction syndrome, e.g., cone dystrophy [10] and rod [11] or blue cone monochromacy [12], also have a normal fundus, and only the findings of full-field ERGs can lead to a correct diagnosis.

The history of occult macular dystrophy (OMD) is slightly different. Patients were found with a progressive decrease in the visual acuity and essentially normal fundus and fluorescein angiographic findings [13–15]. In contrast to the CSNB and cone dysfunction syndrome cases, these patients had normal full-field ERGs. Only after the development of the focal macular ERG [16–20] techniques was it found that these patients had a depression of the macular function. This indicates that the retinal dysfunction is confined only to the macula.

The first account of OMD was published in 1989 under the title "Hereditary macular dystrophy without visible fundus abnormality" [13]. Thereafter, several depictions of patients with similar phenotypes were published [14], and this clinical condition was named, "occult macular dystrophy" in 1996. The term occult was used to mean that the cause of the dystrophy was "hidden from sight".

At first, OMD could only be diagnosed by the results of both full-field ERGs and focal macular ERGs. After multifocal ERGs (mfERGs) were developed [21], patients diagnosed with OMD following the full-field and focal macular ERG findings were found to have a reduction of the amplitudes of the mfERGs recorded from the central areas. With the widespread use of mfERGs, patients worldwide were diagnosed with OMD based on the findings of mfERGs [22–24].

With the development and refinement of optical coherence tomography (OCT), eyes diagnosed with OMD by electrophysiological findings were found to have structural abnormalities in spite of the normal appearance of the macula by ophthalmoscopy [25–30].

The hereditary mode of OMD has been shown to be autosomal dominant in many patients whereas others were classified as sporadic. In 2010, genetic studies detected mutations in the retinitis pigmentosa 1-like 1 (*RP1L1*) gene in an eye with autosomal dominant OMD [31].

The important point clinically is that OMD is not a rare disease and that more advanced electrophysiological and imaging techniques are needed to make a correct diagnosis. Thus, patients with reduced visual acuity and a normal fundus may be misdiagnosed with various diseases other than OMD.

Here we present the history of the discovery of OMD, detailed clinical characteristics, electrophysiological characteristics and genetic information of eyes with OMD.

History of occult macular dystrophy (OMD)

In 1989, Miyake et al. reported on three patients from two generations of the same family with poor visual acuity. The fundi of the three patients appeared normal by ophthalmoscopy and fluorescein angiography, even in the older patient, and the results of full-field electroretinograms were also normal for both the cone and rod components. However, the amplitudes of the focal macular ERGs were severely reduced. This paper was published under the title, "Hereditary macular dystrophy without visible fundus abnormality". The diagnosis of OMD in these patients was made only after the development of the focal macular ERG.

Development of focal macular ERG techniques

The principle of recording focal macular ERGs includes presenting a small stimulus to the macula and recording the response elicited from this area. Several investigators had tried to obtain responses from the macula alone, but the results were not satisfactory because of the strong effect of stray light. Layer-by-layer analysis by recording many components of cone ERG, necessary for routine clinical examinations, was not possible, either. To minimize the effects of stray light responses, background illumination must be used to suppress the sensitivity of the area surrounding the stimulus. It is also important to monitor the location of the stimulus on the fundus during the recording to be certain that only the macula is being stimulated. This is especially true for eyes with macular diseases with a central scotoma.

In 1988, a comprehensive system for recording focal macular ERGs was developed by modifying an infrared television fundus camera. With this system, the a-waves, b-waves, d(off)-waves, oscillatory potentials, photopic negative responses (PhNR) [32], and 30 Hz flicker responses could be accurately recorded exclusively from the human macula (Fig. 1) [16, 17, 19]. Using this system, a layer-by-layer analysis of the retina with different macular diseases could be obtained. The first diagnosis of an OMD patient and detail analyses of the pathogenesis of many OMD patients were accomplished with this system.

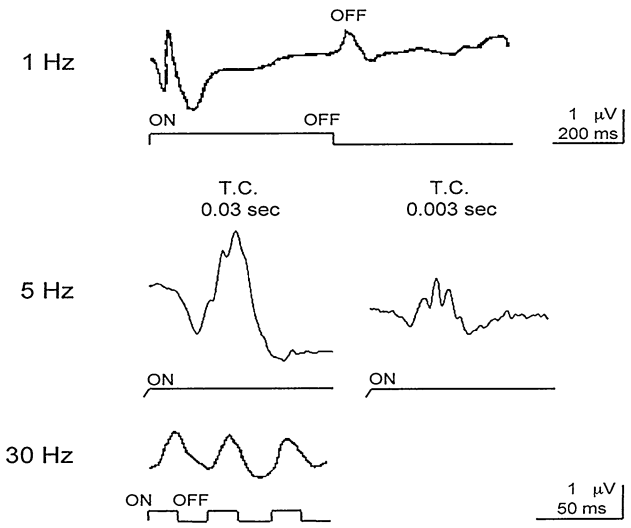

Fig. 1 Components of the focal macular ERGs recorded in a normal subject [16, 19]. The ON and OFF responses recorded with 1-Hz frequency (*top*); *a*-wave and *b*-wave, oscillatory potentials (OPs), and photopic negative response (PhNR) recorded with 5-Hz stimulus frequency (*middle*); and 30-Hz flicker responses (*bottom*) are shown. *TC* time constant

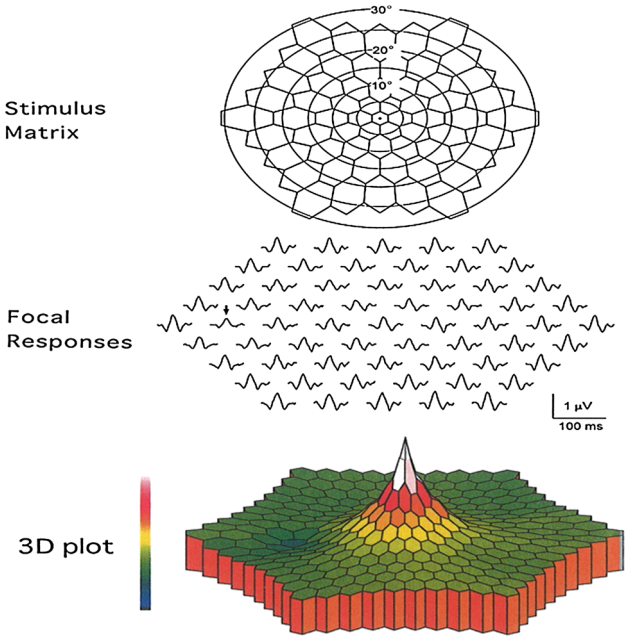

Fig. 2 Stimulus matrix (*top*), multifocal ERG responses (*middle*), and a topographic plot of the amplitudes (*bottom*) of standard multifocal ERG recordings from a normal subject. The *arrow* in the *middle* shows a response from the area around the optic disc

Development of multifocal ERGs

In 1992, 3 years after OMD was firstly reported, a new technique termed multifocal ERG (mfERG) was developed by Sutter and Tan [21]. To record the mfERGs, the retina is stimulated with an array of hexagonal stimuli generated on a computer monitor. The sizes of the hexagons are scaled with eccentricity to elicit approximately equal amplitude responses at all locations. Each hexagon has a 50 % chance of being bright at each frame change. The pattern appears to flicker randomly, but each element follows a fixed, predetermined *m*-sequence so the overall luminance of the screen over time is relatively stable. By correlating the continuous ERG signals with the on and off phases of each stimulus element, the focal ERG signals associated with a specific hexagonal element is recorded. An array of the 103 focal responses of the multifocal ERG and a topographic map of the amplitude of the ERG at each locus are shown in Fig. 2. With this method, ERGs can be recorded simultaneously from multiple focal retinal locations during a single recording session using cross-correlation techniques. Since its introduction it has been used worldwide and many patients with OMD were correctly diagnosed by analyzing the mfERGs [22–24].

Age and visual acuity of OMD patients

The age at which a patient with OMD recognizes a decrease of vision varies widely from as young as 6 to 60 years old. In a study of a large family with thirteen OMD patients (six men and seven women) carrying the p.Arg45Trp mutation (Fig. 3), the age at the onset of visual difficulties varied from 6 to 50 years with a mean of 27.3 ± 15.1 years. The average age at the final examination was 57.2 ± 22.1 years [30]. The duration of the continuous decrease in the visual acuity varied from 10 to 30 years (mean 15.6 ± 7.7) in 16 eyes of 9 adult patients. After this period, the vision did not decrease. All of the patients were affected in both eyes, and the onset was the same in the two eyes except for four patients (cases 1–4) [30]. One patient (case 1) first noticed a decrease in her visual acuity OS at age 50 years, and she still did not have any subjective visual disturbances OD 30 years later. However, a clear decrease in the mfERG in the macular area was detected OU.

The BCVA of OMD patients is occasionally normal or only slightly affected, although the response of focal macular ERG is reduced. In such cases, OCT can demonstrate a small normal morphological region at the fovea.

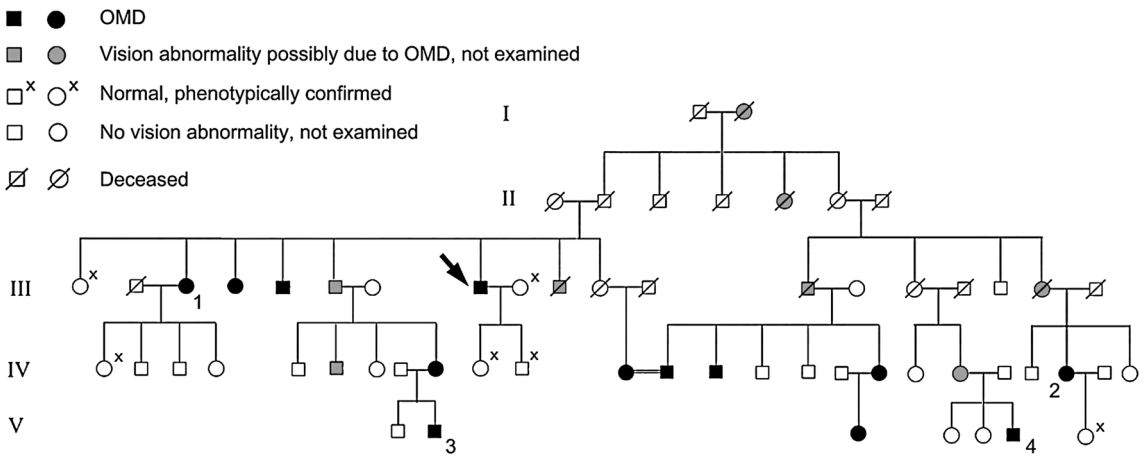

Fig. 3 Pedigree of a family with OMD. All thirteen patients had the *RP1L1* gene mutation (p.Arg45Trp). The proband is indicated by the *arrow*

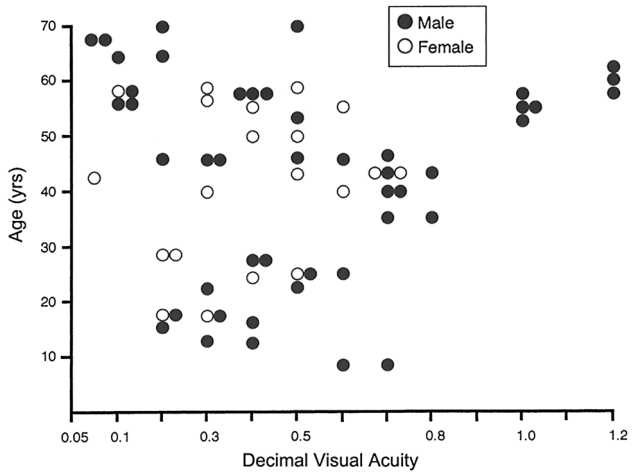

Fig. 4 Distribution of visual acuities (*x*-axis) versus age (*y*-axis) in eyes with OMD [15]. Note that some patients have normal visual acuity. Adapted with permission from Miyake Y. 'Electrodiagnosis of retinal diseases', Tokyo: Springer-Verlag; 2006

The distribution of the visual acuities and age at the initial visit in 33 patients (22 men and 15 women) examined at Nagoya University is shown in Fig. 4 [15]. This graph contains patients from different families, but not all these patients had gene analyses performed. The graph shows that some of the patients had normal visual acuity despite their focal macular ERGs being definitely reduced. There is no obvious correlation between the age at the initial visit and the visual acuity.

Fundus findings and fundus autofluorescence images

Three fundus photographs and fluorescein angiograms from one family with OMD are shown in Fig. 5 [13]. They are essentially normal. The fundus autofluorescence (AF) images were also essentially normal in the entire posterior pole (Fig. 6a). However, some cases ($\sim$50 % of patients with the *RP1L1* mutation) have been shown to have a circular area with increased AF signal at the fovea [33]. This area of increased AF is very faint in some cases (Fig. 6b arrow) and more apparent in others (Fig. 6c, arrow). These findings imply that the primary lesion of OMD is in the photoreceptors rather than the RPE. The AF abnormalities in eyes with OMD are very different from other macular dystrophies and cone-rod dystrophies, which have distinctive patterns of AF. The relationship between duration of the disease and intensity of the increased AF signal has not been confirmed.

Electroretinograms (ERGs)

The full-field ERGs recorded with the ISCEV standard protocol are normal for both the rod and cone components in patients with OMD; however, some patients may show slightly reduced cone ERGs. The amplitudes and implicit times of the focal macular ERGs are markedly reduced and delayed, and the mfERGs are reduced in the central areas. The findings of full-field ERGs and focal macular ERGs recorded with three diameter spot sizes (5°, 10°, and 15°) in a typical patient with OMD are shown in Fig. 7.

Many OMD patients have non-detectable focal macular ERGs when the stimulus spot is small. However, when the stimulus spot is relatively large (10° or 15° in diameter), a response is recordable but is significantly smaller than normal (Fig. 8). The waveform of the response is often a small *a*-wave with a relatively large *b*-wave [23]. The cone ERGs recorded with long duration stimuli are classified as having a depolarizing pattern response which is similar to that recorded when the ON-bipolar cell is predominantly functioning [34]. These results suggest that the OFF visual pathway is more severely affected in the macula in eyes with OMD.

A three-dimensional topographic map of the mfERGs is shown in Fig. 9. The averaged waveforms of the multifocal ERGs for the different eccentric rings in 20 normal subjects and 8 patients with OMD are superimposed [23]. The differences in the amplitudes of the ERGs recorded from patients with OMD and from normal subjects become smaller toward the peripheral field. Most OMD patients have slight but significantly longer implicit times than those of normal controls across the whole testing field. These longer implicit times suggest that the retinal dysfunction has a broader extent than expected from the ERG amplitudes and psychophysical perimetric results (see below).

Two-color (cone-rod) perimetry in macula

Light-adapted (cone) and dark-adapted (rod) two-color perimetry is useful in the independent evaluation of the cone and rod visual pathways. This was originally designed by Jacobson and associates and is performed with a modified Humphrey Field Analyzer [35]. Only the function of the posterior pole was measured in our series [14]. Profile plots of cone-rod perimetry in a representative OMD patient (case 1) and cone perimetry in another OMD patient (case 2) are shown in Fig. 10. The visual acuity of case 1 was 0.2 and of case 2, 1.0. In each profile, the normal variations (mean $\pm$ 2 SD) of 30 normal subjects are shown as the range surrounded by the two dotted lines. The normal sensitivity level for the light-adapted test is at least 15 dB at all test points with higher levels near the center of the visual field. The light-adapted results indicate abnormal sensitivities only at the fovea. The normal dark-adapted sensitivity for the 500-nm target was approximately 70 dB

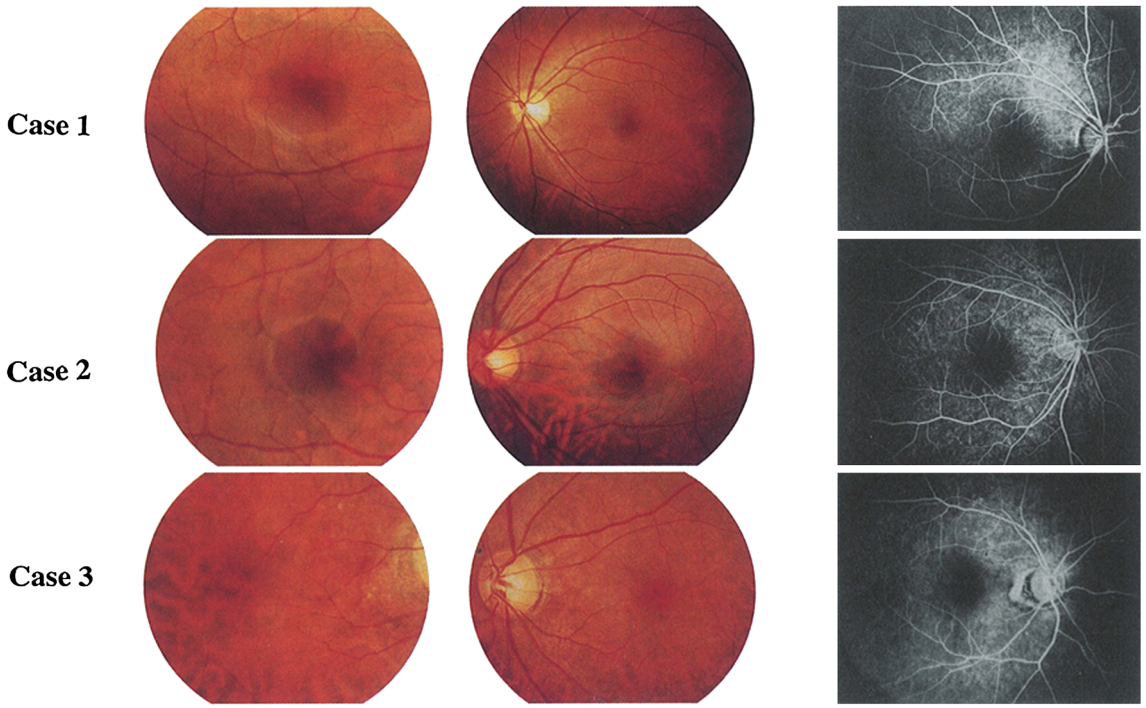

Fig. 5 Fundus photographs (*left*) and fluorescein angiograms (*right*) of three patients with OMD from a single family [15]. Cases 1, 2, and 3 are a 29-year-old woman, a 19-year-old man, and a 55-year-old-man, respectively. Case 3 is the father of cases 1 and 2. All three patients had the *RP1L1* gene mutation [31]. Adapted with permission from Miyake Y. 'Electrodiagnosis of retinal diseases', Tokyo: Springer-Verlag; 2006

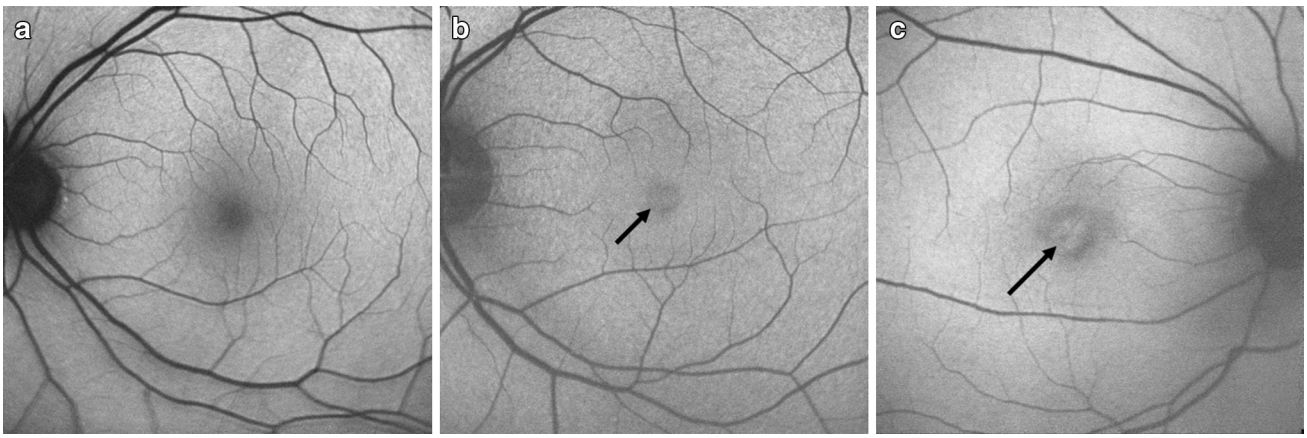

Fig. 6 Fundus autofluorescence (AF) images in three OMD patients with *RP1L1* mutation (p.Arg45Trp, heterozygous). **a** A 32-year-old woman with normal AF image. **b** A 30-year-old man showing faint increased AF at the fovea (*arrow*). **c** A 71-year-old woman showing a mildly increased AF signal at the fovea without a distinct border (*arrow*). All the AF images were recorded with a 488-nm wavelength using a barrier filter for the detection of emitted light above 500 nm (HRA2; Heidelberg Engineering, Heidelberg, Germany)

with the lower level at the fovea, and approximately 40 dB for the 650-nm target. When the red (560-nm) and blue-green (500-nm) targets are adjusted for equal energy, the rod photoreceptor system will be 26 dB more sensitive to blue-green than to red, whereas cones will show only 8 dB greater sensitivity to blue–green than to red. Therefore, a sensitivity difference of approximately 26 dB indicates a rod-mediated detection, whereas a difference of approximately 6 dB means a cone-mediated detection. The sensitivity differences of between 8 and 26 dB suggest mixed rod and cone detection: rods detect the blue–green stimulus and cones the red stimulus. Based on these criteria, the macular cone sensitivity is depressed but rod sensitivity is normal in case 1. In case 2, the macular cone

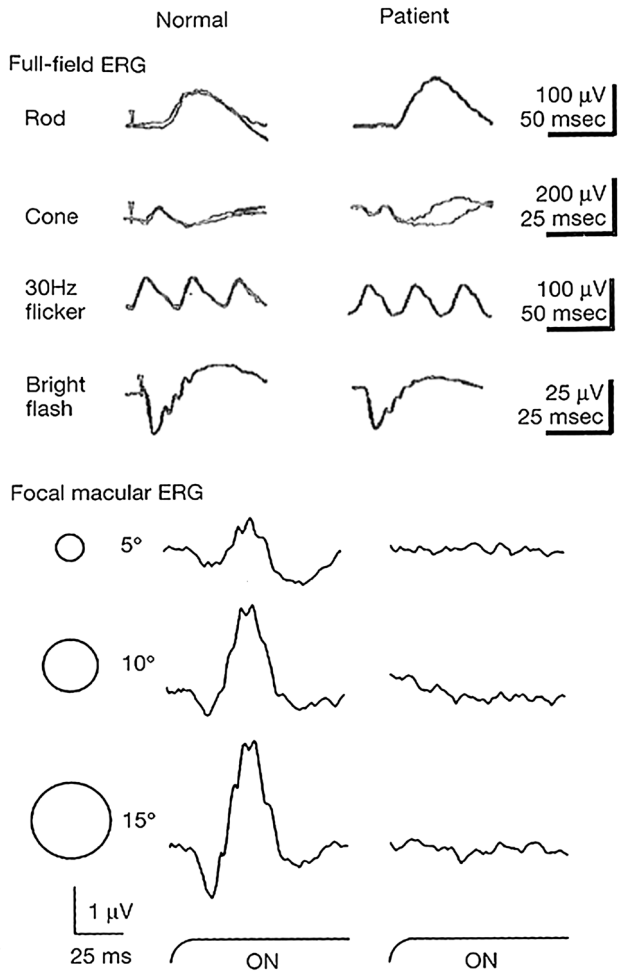

Fig. 7 Full-field ERGs (*upper*) and focal macular ERGs elicited by three spots of different sizes (5°, 10°, 15°in diameter) (*lower*) in an OMD patient

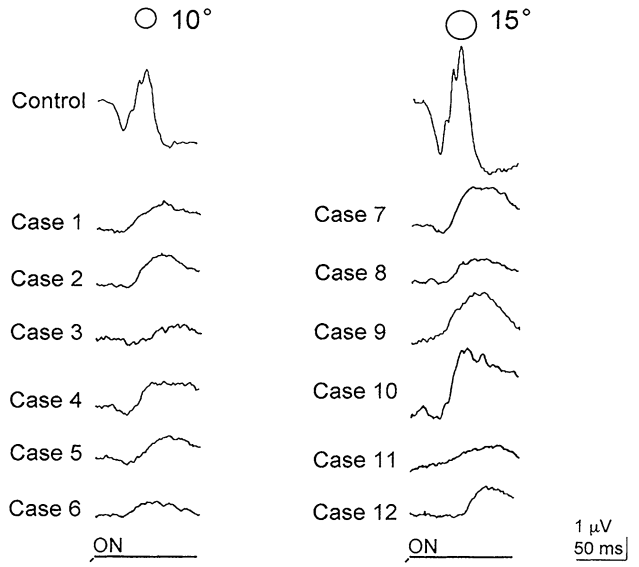

Fig. 8 Focal macular ERGs elicited by 10° or 15° stimulus from OMD patients. The waveform of the focal macular ERGs is a depolarizing pattern with a small *a*-wave, if any, and a relatively large *b*-wave [15]. Adapted with permission from Miyake Y. 'Electrodiagnosis of retinal diseases', Tokyo: Springer-Verlag; 2006

sensitivity is severely depressed, but a small area of the fovea has good sensitivity, resulting in normal visual acuity.

In our series of 13 patients with OMD who underwent this two-color perimetric testing, a loss in the sensitivity of the cone system in the macula was detected in all patients. The sensitivity of the macular rod system was normal in six patients (group 1), and borderline or abnormal in six patients (group 2). The average age of the patients was 30.2 years in group 1 and 58 years in group 2 ($P < 0.05$). These results suggest that only the cone system is abnormal in the relatively early stage, and the rod system is impaired in older patients.

Some patients have normal visual acuity in spite of having abnormal focal macular ERGs or multifocal ERGs (see case 2). This apparent discrepancy can be resolved by examining the cone sensitivity profile in Fig. 10. The patients with good visual acuity also had decreased cone sensitivity in the macula, but the function of one point in the foveola may still be relatively well preserved. It may be that the small center of the fovea in such patients functions well and accounts for the good visual acuity. The parafovea, however, is dysfunctional, resulting in the low amplitude in focal macular ERGs.

Optical coherence tomography

Spectral-domain OCT is a very important method in the diagnosis of OMD [30]. In patients with the *RP1L1* mutation, the most prominent features on OCT are the abnormalities of the two highly reflective lines in the OCT images at the macula.

These lines correspond to the ellipsoid region of the photoreceptor inner segments (ISe) and cone outer segment tips (COST) line (Fig. 11). The ISe line at the fovea appears thickened and blurred in the early stages of OMD and disrupted or absent in the later stages. The COST line cannot be clearly observed in the macular area even in the early stage. In the peri-macular regions which have normal visual function, all the outer retinal microstructures are normal. In longer duration cases, e.g., >30 years, both the photoreceptor and outer nuclear layers are thinnest at the macula; however, the retinal pigment epithelium remains unchanged (Fig. 11). The location of the COST line coincides with the location where the outer segment cone discs are renewed [36, 37], and the ISe line coincides with the

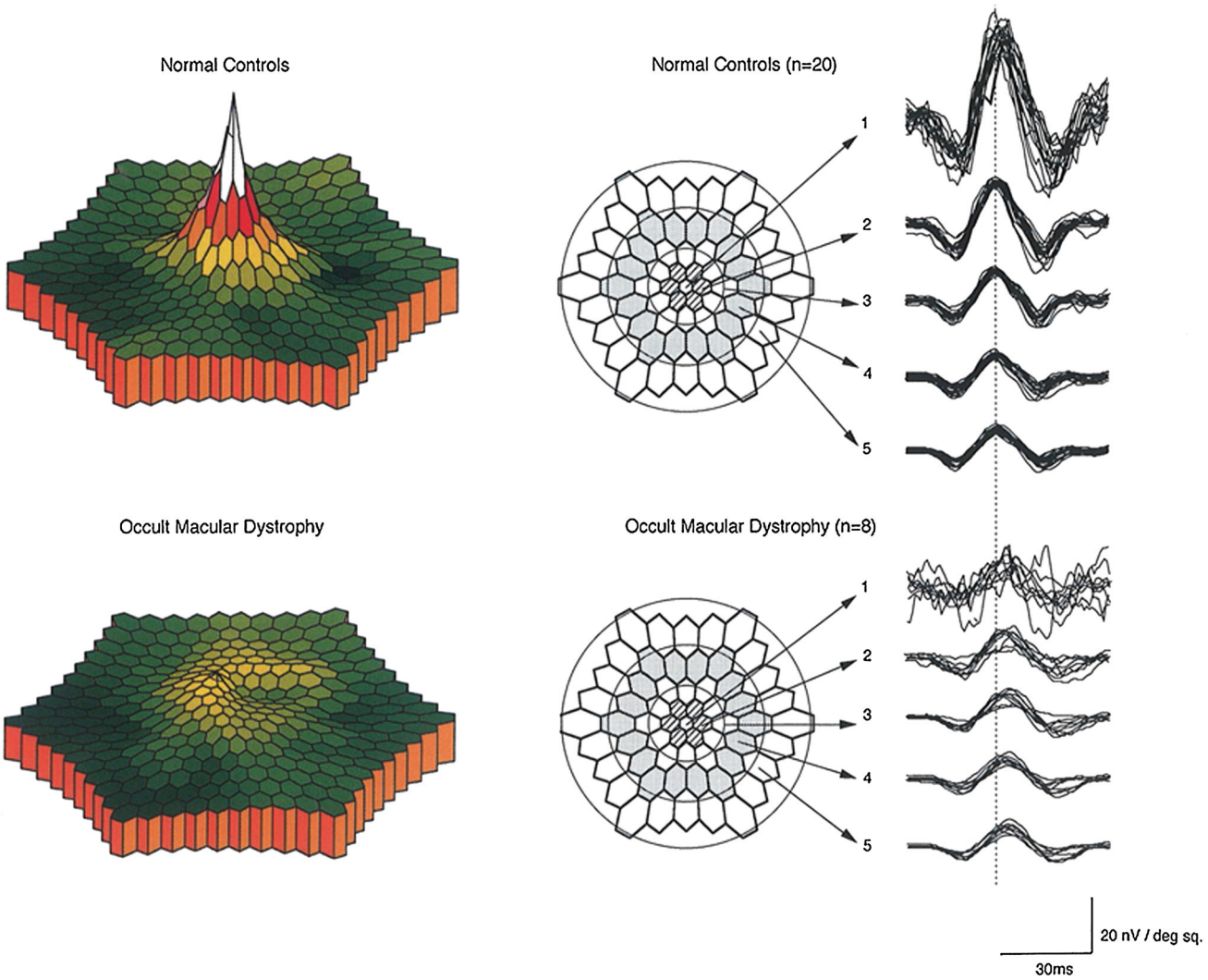

Fig. 9 Three-dimensional topographic map (*left*) and averaged waveform (*right*) of multifocal ERGs for five eccentric rings in a normal subject and an OMD patient [23]. Responses for 20 normal subjects and eight OMD patients are superimposed in the averaged waveforms. The *vertical dotted line* indicates an implicit time of 29.4 ms. Adapted with permission from Miyake Y. 'Electrodiagnosis of retinal diseases', Tokyo: Springer-Verlag; 2006

region which is rich in mitochondria that play important roles in cellular metabolism [38]. The disappearance or blurring of both COST and ISe lines thus indicates an early stage of dysfunction of the cone photoreceptors.

The OCT images of sporadic cases of OMD without the *RP1L1* mutation, on the other hand, do not resemble those of patients with the *RP1L1* mutation. For example, some have a normal ISe line at the fovea, some a clearly localized disruption of the ISe line at the fovea, and some a minimally disrupted COST line at the fovea [30]. Considering that the OCT abnormalities in sporadic cases do not show similar patterns to patients with the *RP1L1* mutation, the electrophysiologically confirmed OMD eyes surely consist of diseases with multiple independent etiologies.

Genetics

In 2010, linkage analyses in two OMD families with dominant inheritance patterns showed that mutations in the *RP1L1* gene located in the short arm of chromosome 8 were responsible for the OMD [31]. The cases with this mutation have been reported to share the same clinical features, especially the OCT images [30]. Recently, a number of cases of OMD with *RP1L* gene mutations have been reported [31, 39–42], and all of them had heterozygous missense mutations: the most common mutation was p.Arg45Trp in exon 2.

The *RP1L1* gene was originally cloned as a gene derived from common ancestors with the retinitis pigmentosa 1 (*RP1)* gene, which is responsible for 5–10 % of autosomal dominant retinitis pigmentosa (RP) worldwide. It is located

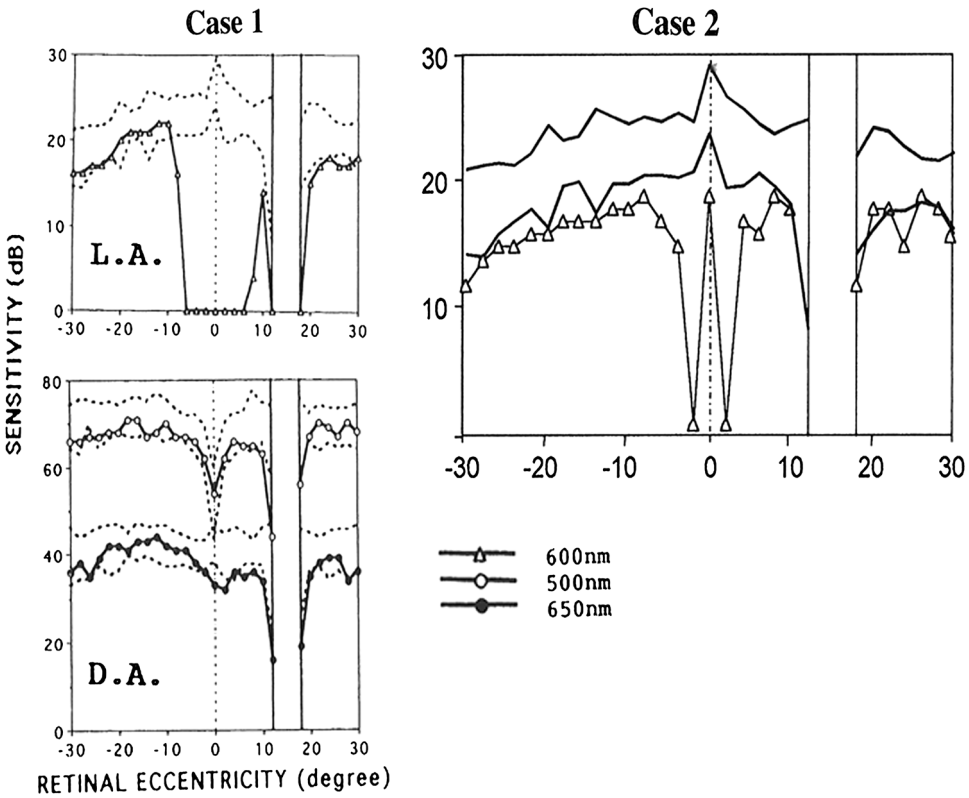

Fig. 10 Results of two-color perimetry. Rod-cone perimetry (*left*) and cone perimetry (*right*) in two patients with OMD. The visual acuity of cases 1 and 2 are 0.2 and 1.0, respectively. In case 1, the macular cone sensitivity is depressed severely, but macular rod sensitivity is within the normal range. In case 2, the macular cone sensitivity is depressed, but only a small area of the fovea has good sensitivity. The *dotted lines* (*left*) and *solid lines* (*right*) indicate the normal range. Adapted with permission from Miyake Y. 'Electrodiagnosis of retinal diseases', Tokyo: Springer-Verlag; 2006

on the same chromosome 8 [43–47]. An immunohistochemical study on cynomolgus monkeys showed that *RP1L1* was expressed in rod and cone photoreceptors, and it is believed to play important roles in the morphogenesis of the photoreceptors [43, 48]. Heterozygous *RP1L1* knock-out mice were reported to have normal retinal morphology while homozygous knock-out mice developed subtle retinal degeneration [48]. However, the RP1L1 protein has a very low degree of overall sequence identity (39 %) between humans and mice compared to the average values of sequence similarity observed between human and mice proteins. The cellular mechanisms that explain why only the macular region is impaired in human OMD patients have not been determined.

In the Japanese population, *RP1L1* gene mutations are rarely found in sporadic cases. There are OMD families without the *RP1L1* mutation where autosomal recessive inheritance is assumed. The genetic background leading to the OMD may be a variant, and other genetic causes will probably be determined in future studies.

Course of OMD

The correlation between age and visual acuity at the initial visit was not significant. In addition, the visual acuity of the older OMD patients in the same families was not always lower than those of the younger patients. These findings suggest that the age of onset and the speed of progression vary widely among patients even in the same family.

OMD is progressive in nature judging from the history of patients. However, only a few reports follow the eyes of OMD patients for a long period. The first patient diagnosed with OMD was a 29-year-old woman who was examined by one of the authors (YM) in 1986. Her fundus and fluorescein angiograms are still normal in 2014 although the visual acuity OU has decreased slightly.

Differential diagnosis

We believe that OMD may not be as rare as was originally thought. Before focal macular ERGs and mfERGs were used as routine clinical tests, many patients with OMD were probably misdiagnosed as having other diseases with low visual acuity and normal fundus. Because of the normal fundus appearances and normal full-field ERGs, OMD was often misdiagnosed as optic neuropathy of unknown origin, amblyopia, or non-organic visual loss. There were also cases with a diagnosis of senile cataract which were later diagnosed as OMD because the low visual acuity remained after the cataract surgery.

Cone dystrophy is a hereditary retinal dystrophy with progressive decrease of visual functions. Some of the

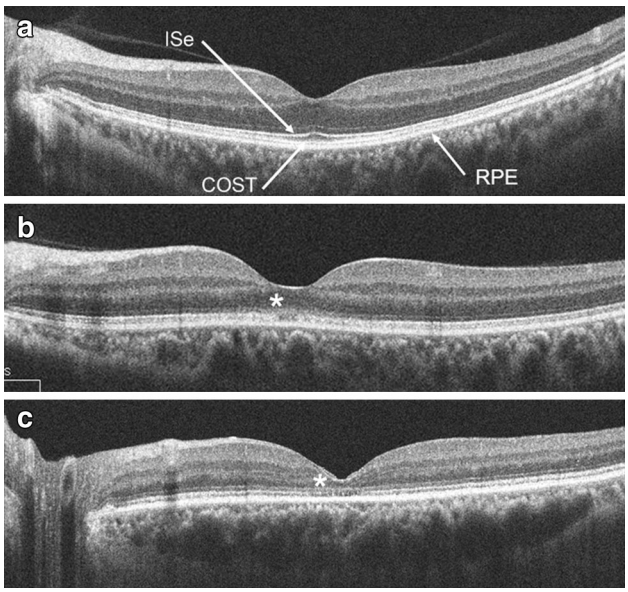

Fig. 11 OCT images from two OMD patients with *RP1L1* mutation (p.Arg45Trp, heterozygous). **a** OCT image of a normal control without the *RP1L1* mutation (40-year-old man). All of the outer retinal structures, including ellipsoid of photoreceptor inner segment (ISe) line, cone outer segment tip (COST) line, and retinal pigment epithelium (RPE), are clearly observed both in the fovea and the peri-macular region. **b** A 30-year-old man. The COST line is not present over the entire macula but is present in the peri-macular regions. The ISe line is blurred at the fovea (*asterisk*), but clearly observed in the peri-macular regions. The RPE is normal in the entire region. **c** An 83-year-old man. The COST line cannot be seen in the macula but is still visible in the peri-macular region. The ISe line is disrupted at the fovea (*asterisk*). There is an apparent thinning of the photoreceptor layer at the fovea. The RPE is normal in the entire region

patients with cone dystrophy may have normal fundus appearance [10]; however, eyes with cone dystrophy always have abnormal or absent full-field cone ERG as well as absent focal macular ERG. Congenital stationary night blindness with normal fundus is a hereditary retinal disease which is classified into two different clinical entities, complete and incomplete types [4]. This classification has been verified by molecular genetics analysis [5–9]. Most patients with both types often have moderate disturbances of visual acuity associated with high myopia or hyperopia from a young age. Some patients may not complain of night blindness, especially those with the incomplete type of CSNB [35]. Thus, a differential diagnosis of OMD is required. The full-field ERGs of both types show unique abnormalities [4, 49].

Future studies of OMD

In OMD patients, only the macular region is affected while other retinal regions remain normal functionally and morphologically, even at a very advanced stage. Moreover, the fundus appearance and retinal pigment epithelium remain intact until the end stage while the photoreceptor layer in the macular area is markedly damaged. Functionally, ON bipolar function is relatively preserved in macula of OMD patients with a depolarizing pattern in the focal macular ERGs. This finding may be related to a red–green color vision defect which was often observed in such OMD patients [15]. Also, the relative preservation of rod function in the macula may be from the result of some remodeling of the synapse from cone synapses to the ON synapses of rods.

These are still some important mysteries peculiar to OMD and not observed in other macular dystrophies. The *RP1L1* gene in humans has only 40 % homology with that of mice, and its cellular function in the primate's macula has not been determined. More detailed investigations on the function of *RP1L1* should provide information to answer these questions.

Acknowledgments This research was supported by (1) research grants from the Ministry of Health, Labor and Welfare, Japan and (2) Grant-in-Aid for Scientific Research, Japan Society for the Promotion of Science, Japan. This manuscript was edited by Prof. Duco Hamasaki of the Bascom Palmer Institute.

Conflicts of interest Y. Miyake, None; K. Tsunoda, None.

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