Visual Field Characteristics in East Asian Patients With Occult Macular Dystrophy (Miyake Disease): EAOMD Report No. 3

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PURPOSE. The purpose of this study was to investigate the perimetric features and their associations with structural and functional features in patients with RP1L1-associated occult macular dystrophy (OMD; i.e. Miyake disease).

METHODS. In this international, multicenter, retrospective cohort study, 76 eyes of 38 patients from an East Asian cohort of patients with RP1L1-associated OMD were recruited. Visual field tests were performed using standard automated perimetry, and the patients were classified into three perimetric groups based on the visual field findings: central scotoma, other scotomata (e.g. paracentral scotoma), and no scotoma. The association of the structural and functional findings with the perimetric findings was evaluated.

RESULTS. Fifty-four eyes (71.1%) showed central scotoma, 14 (18.4%) had other scotomata, and 8 (10.5%) had no scotoma. Central scotoma was mostly noted in both eyes (96.3%) and within the central 10 degrees (90.7%). Among the three perimetric groups, there were significant differences in visual symptoms, best-corrected visual acuity (BCVA), and structural phenotypes (i.e. severity of photoreceptor changes). The central scotoma group showed worse BCVA often with severe structural abnormalities (96.3%) and a pathogenic variant of p.R45W (72.2%). The multifocal electroretinogram (mfERG) groups largely corresponded with the perimetric groups; however, 8 (10.5%) of 76 eyes showed mfERG abnormalities preceding typical central scotoma.

CONCLUSIONS. The patterns of scotoma with different clinical severity were first identified in occult macular dystrophy, and central scotoma, a severe pattern, was most frequently observed. These perimetric patterns were associated with the severity of BCVA, structural phenotypes, genotype, and objective functional characteristics which may precede in some cases.

Keywords: Miyake disease, occult macular dystrophy, RP1L1, visual fields

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Occult macular dystrophy (OMD; OMIM: 613587), first described by Miyake et al., is an inherited type of macular dystrophy characterized by progressive visual loss in the eyes with an essentially normal-appearing fundus and normal full-field electroretinogram.\(^1\)\(^-\)\(^3\) In successive studies, \(RP1LI\) was identified as a causative gene,\(^4\) and several pathogenic variants showing autosomal dominant inheritance, including p.R45W and residues 1196 to 1201 downstream of the doublecortin domain, have been reported.\(^5\)\(^-\)\(^8\) Structural changes in the photoreceptors, such as disruption or loss of the ellipsoid zone or interdigitation zone, have been reported using high-resolution retinal imaging, such as spectral-domain optical coherence tomography, in patients with OMD.\(^5\)\(^-\)\(^10\)

The East Asia Inherited Retinal Disease Society (EAIRDs: https://www.eairds.org/) was established in 2016 to investigate the clinical and genetic characteristics of inherited retinal diseases in the East Asian population, and the East Asian OMD (EAOMD) study was the first project.\(^8\) Previous EAOMD reports demonstrated the clinical and genetic characteristics as well as the electrophysiological features in East Asian patients with OMD.\(^8\)\(^,\)\(^11\) These reports showed a large spectrum of these characteristics in patients with OMD harboring pathogenic \(RP1LI\) variants (i.e. Miyake disease).\(^8\)\(^,\)\(^11\)

Given the essentially normal fundus, assessment of the subjective visual function by a visual field test is important to evaluate the functional defect and its degree or severity and may be as important as objective tests, such as optical coherence tomography (OCT) and electroretinography (ERG), which are essential for diagnosis of OMD. Miyake et al. reported in 2004 that light-adapted and dark-adapted perimetry illustrated loss of cone sensitivity in the macula and the variable changes of rod sensitivity in the macula in 12 patients with OMD.\(^2\) However, since then, few reports have described the perimetric findings, including central scotoma and even normal findings in patients with OMD, although visual field tests are widely performed for the documentation of decreased central vision and for the diagnosis of OMD.\(^9\)\(^,\)\(^11\)

Thus, the clinical value of automated perimetry for the diagnosis of OMD is still unclear, and the structural or functional correlation with other modalities has not been evaluated. Accordingly, in this multicenter study, we investigated the perimetric findings in patients with Miyake disease and evaluated their correlations with clinical, genetic, structural, and functional findings. From the analyses, we intended to address the role of automated perimetry in the clinical evaluation of OMD.

**Methods**

**Patients**

We included patients with a clinical diagnosis of OMD at participating centers for EAOMD studies of EAIRDs from Japan, China, and South Korea enrolled between June 1, 2016, and December 31, 2020. Of 101 patients initially included with a clinical diagnosis of OMD, which had been made by the attending doctors and confirmed by three principal investigators (authors K.F., S.J.W., and R.S.), 46 patients with pathogenic variants in the \(RP1LI\) gene were identified. All subjects met the criteria for Miyake disease: (1) presence of macular dysfunction; (2) no fundus abnormalities confirmed on fundoscopy; and (3) detection of a pathogenic \(RP1LI\) variant.\(^8\) Among these patients, those without standard automated perimetry (\(n = 6\)) and those without reliable perimetric results (\(n = 2\)) were excluded. Finally, a cohort of 76 eyes of 38 patients was established for the analysis. All the clinical data, images, and genetic data were uploaded to the international EAOMD database, and the data quality and conclusive diagnoses were confirmed by the three principal investigators (authors K.F., S.J.W., and R.S.).

This study was approved by the institutional review boards of the participating institutions from Japan, China, and South Korea: National Institute of Sensory Organs, National Hospital Organization, Tokyo Medical Center, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, and Seoul National University Bundang Hospital, and adhered to the tenets of the Declaration of Helsinki. Signed informed consent was obtained from all study participants.

**Patient Evaluation**

In addition to obtaining the detailed medical and family history, we performed comprehensive ophthalmic examinations for all patients, including best-corrected visual acuity (BCVA) assessment, slit-lamp examination, fundus examination, fundus photography, OCT, and visual field testing. Spectral-domain OCT (SD-OCT) was performed using Spectralis (Heidelberg Engineering, Heidelberg, Germany) or Cirrus high-definition (HD) OCT (version 7.5; Carl Zeiss Meditec, Dublin, CA, USA) in the participating hospitals.\(^8\) Confocal scanning laser ophthalmoscopy (Heidelberg Retina Angiograph; Heidelberg Engineering) was used to obtain fundus autofluorescence (FAF) or infrared reflectance images.\(^8\) Electrophysiological assessments included focal macular electroretinogram, multifocal electroretinogram (mfERG) and/or full-field ERG, which was performed according to the standards of the International Society for Clinical Electrophysiology of Vision.\(^12\)\(^-\)\(^14\) The details of the equipment are described in our previous reports.\(^8\)\(^,\)\(^11\)

We performed standard automated perimetry using the 30-2/24-2 or 10-2 strategies of the Humphrey Field Analyzer (HFA, Model 750i and 750; Carl Zeiss Meditec) or Octopus 101 perimeter (Haag-Streit, Koeniz, Switzerland). Using the reliability indices of fixation losses (>20%) and false-positives (>15%) and negatives (<15%), we excluded unreliable results from our analyses.\(^15\) The patterns of
scotoma on the pattern deviation plot of the Humphrey visual field (HVF) test results were judged by an independent investigator (author S.J.A.) who was blinded to the clinical information. Global indices of HVF, such as the mean deviation (MD) and pattern standard deviation (PSD), were also used for the quantitative analyses, which were separately performed for each of the 10-2 and 30-2 results.

**Perimetric Group Classification**

We also classified the eyes into three perimetric groups according to the patterns observed from the pattern deviation maps of the HVF, as shown in Figure 1: the central scotoma (decreased foveal sensitivity and/or decreased parfoveal sensitivity), other scotoma (relatively preserved foveal sensitivity and scotoma outside of the central field, such as paracentral scotoma), and no scotoma groups.

**Morphological Phenotype and Functional Group**

Based on the morphologic features on the OCT B-scans and spatial characteristics on mERG, the patients were classified into microstructural and mERG functional groups, as performed in previous studies. More specifically, the eyes were grouped into two subtypes according to the severity of the SD-OCT morphologic phenotypes: (1) severe phenotype (a classic phenotype compatible with stages Ia, Ib, IIa, IIIa, and IIIb) showing both a blurred/flat ellipsoid zone (EZ) and the absence of the interdigitation zone (IZ); (2) mild phenotype (subtle morphologic changes compatible with stages Ia and Ib) defined as minimal or local blurring of the EZ and local absence of the IZ. The mERG abnormalities were evaluated based on the normal reference values (supplementary material in EAOMD Report No. 21). Based on the spatial variation determined by an expert's careful examination of the traces, the eyes were also grouped into three functional groups, as described in our previous study: (1) paracentral dysfunction with relatively preserved central/peripheral function, (2) homogeneous central/paracentral dysfunction, and (3) widespread dysfunction over the whole area tested.

**Genotype**

Genetic screening for causative genes was performed using blood samples from the subjects in the participating centers. Whole-exome sequencing with targeted analysis, next-generation sequencing with a targeted capture panel or direct sequencing was performed, as described in detail in previous reports. Detected pathogenic RP1L1 variants were classified into two groups: hot spot 1 (c.133C>T, p.R45W)) and hot spot 2 (amino acids 1196–1201).

**Analyses**

All continuous variables are presented as the mean ± standard deviations. Descriptive statistics were used for the demographic and clinical data and perimetric findings. To evaluate the topographic location of scotoma, pointwise frequency map of scotoma was generated by calculating the proportion of scotoma at each test point in pattern deviation maps of 10-2 and 30-2 HVF tests and representing the data in a grayscale using MATLAB software 2021a (MathWorks, Inc., Natick, MA, USA). The frequencies of all the test points in the left eye images were converted to the right-eye format by matching identical test locations, leading to one frequency for each test location. The clinical and genetic characteristics were compared among the three perimetric groups. The comparative analyses among the groups were performed using the Kruskal–Wallis test or Fisher's exact test, depending on the type of clinical variables. Pearson correlation analyses were performed to evaluate the association between the perimetric parameters and BCVA. Statistical analyses were performed using SPSS software version 26 (IBM Corp., Armonk, NY, USA). Statistical significance was set at P values of < 0.05.

**RESULTS**

**Clinical Characteristics of the Study Population**

Table 1 depicts the demographic and clinical characteristics of the 38 patients: 23 men and 15 women from 24 families. The mean age at onset and at the latest examination was 31.2 ± 19.6 and 51.0 ± 18.9 years, respectively. The BCVA in the included eyes was 0.55 ± 0.33 logMAR on average, ranging from −0.08 to 1.22 logMAR. Most of the patients (92.1%) were asymptomatic, whereas the asymptomatic patients were relatives of symptomatic patients who were ascertained to carry the same pathogenic RP1L1 variants. Twenty-two (57.9%) and 16 (42.1%) patients underwent 10-2 and 24-2/30-2 examinations, respectively.

Table 1 also shows the genetic characteristics of the included patients, all with RP1L1 variants. Twenty-three patients (59.0%) had hot spot 1 (c.133C>T, p.R45W) and 14 patients (35.9%) had hot spot 2 (amino acids 1196–1201).

**Visual Field Findings**

Three patterns were observed in the included patients with Miyake disease: central scotoma, other scotoma, and no scotoma. Most of the patients (34 of 38, 89.5%) showed bilateral symmetry in the perimetric findings, with the same patterns in both eyes. Particularly, 26 of 27 patients (96.3%) showing central scotoma showed this scotoma in both eyes. Photographic examples of the three patterns are presented in Figure 1. Central scotoma (see Fig. 1A) was the most common pattern, as noted in 54 of 76 (71.1%) eyes, followed by other patterns (n = 14, 18.4%) and no scotoma (n = 8, 10.5%; see Fig. 1B). Other patterns included paracentral scotoma (see Figs. 1C, 1D; n = 6), superior or inferior arcuate scotoma with or without central scotoma (see Fig. 1E; n = 4), and those not specific for pattern definition (see Fig. 1F; n = 3). Pointwise frequency maps of scotoma (Fig. 2) indicate highest frequency of scotoma in the central area of pattern deviation maps in both 10-2 and 30-2 tests. The detection rates of visual field defects by standard automated perimetry were 71.1% and 89.5% when characteristic central scotoma and any visual field abnormality were used for the definition of positivity, respectively. In the included eyes, the mean MD values in the HVF 10-2 and 30-2 tests were -2.10 ± 2.59 and -3.15 ± 2.49 dB, respectively, whereas those of PSD were 2.04 ± 1.55 and 3.69 ± 1.60 dB, respectively.

**Clinical and Genetic Characteristics of the Three Perimetric Groups**

Table 2 shows the comparison of the clinical characteristics among the three groups divided according to the perimet-
FIGURE 1. Clinical images and perimetric results of representative cases from the three perimetric groups: (A) central scotoma, (B) no scotoma, and (C to F) other scotomata. For all cases, fundus autofluorescence (FAF; top left), fundus photograph (Fd; top center), and optical coherence tomography (OCT; top right), visual fields (bottom left), and multifocal electroretinogram (mfERG; bottom right) are presented. The numbers on the top left corner of visual fields denote the protocols used. Arrowheads indicate hyperautofluorescence within normal foveal hypoautofluorescence.

ric results. Age of onset was significantly different among the perimetric groups. There were also significant differences in the BCVA, MD, and PSD in the 10-2 test, indicating worse visual acuities and global indices in the central scotoma or other scotomata group than in the no scotoma group.

Regarding genetic characteristics, the frequencies of the recurrent variant (c.133C>T, (p. R45W)) were significantly different among the three groups ($P < 0.001$); the variant was more frequently noted in the central scotoma group and rare in the other groups. There were significant differences in the proportions of the perimetric groups between
Visual Field Findings of Occult Macular Dystrophy

### TABLE 1. Clinical and Genetic Characteristics of the Included Patients With Occult Macular Dystrophy Caused by Pathogenic \textit{RP1L1} Variants (Miyake Disease)

| Characteristics                                              | Values (Range)                                                                 |
|---------------------------------------------------------------|-------------------------------------------------------------------------------|
| Age, y                                                        | 51.0 ± 18.9 (17–86)                                                          |
| Sex, male: female                                            | 23 (60.5%):15 (39.5%)                                                         |
| Age of onset, y                                               | 31.2 ± 19.6 (2–73)                                                            |
| Spherical equivalent, diopters                               | −3.13 ± 3.00 (−10.0–1.50)                                                     |
| Best-corrected visual acuity, logMAR                         | 0.55 ± 0.33 (−0.08–1.22)                                                      |
| Symptoms                                                      | Reduced or poor visual acuity (89.5%), photophobia (44.7%), color vision abnormality (2.6%), night blindness (5.3%), no symptom (7.9%) |
| Devices used for standard automated perimetry               | Humphrey Field Analyzer (29, 76.3%), Octopus (9, 23.7%)                      |
| Visual field tests performed, 10-2: 24-2/30-2 (%)            | 22 (57.9%):16 (42.1%)                                                         |
| Visual field patterns (eyes, %)                              | Central scotoma (n = 54, 71.1%), other scotomata (n = 14, 18.4%), no scotoma (n = 8, 10.5%) |
| Mean deviation, dB in 10-2                                   | −2.10 ± 2.59 (−11.25 to −0.46)                                                |
| Mean deviation, dB in 30-2                                   | −3.15 ± 2.49 (−11.22 to −0.63)                                                |
| Pattern standard deviation, dB in 10-2                       | 2.04 ± 1.55 (0.97–8.73)                                                       |
| Pattern standard deviation, dB in 30-2                       | 3.69 ± 1.60 (2.07–9.96)                                                       |
| Pathogenic \textit{RP1L1} variants (n, %)                    | p.Arg45Trp (n = 23, 60.5%), p.Ser1199Cys (n = 10, 26.3%), p.Gly1200Asp (n = 2, 5.3%), p.Ser1198Phe (n = 2, 5.3%), p.Thr1194Met/p.Thr1196Ile (n = 1, 2.6%) |

* Other scotomas included paracentral (n = 6), superior or inferior arcuate scotoma (n = 4), nonspecific abnormality (n = 3), and nasal step (n = 1).

**FIGURE 2.** Pointwise frequency map of scotoma for pattern deviation maps of 10-2 (left) and 30-2 (right). The frequency of scotoma for each test location is shown as a grayscale from white (zero frequency) to black (highest frequency).

The pathogenic variants in hot spot 1 (central scotoma: other scotoma: no scotoma = 39:5:2) and 2 (15:9:4; \( P = 0.011 \)), which also indicates predominance of central scotoma in the patients with the hot spot 1 pathogenic variant. Supplementary Figure S1 summarizes the perimetric parameters of the different genotypes, suggesting a genotype-phenotype association. The eyes of the patients with the pathogenic variants p.R45W and p.S1199C showed generally worse MDs, −3.35 ± 2.77 and −3.19 ± 2.19 dB on the 30-2 test and −1.54 ± 1.48 and −3.88 ± 3.73 dB on the 10-2 test, respectively, and the parameters were similar between pathogenic variants in hot spots 1 and 2 (all \( P > 0.05 \)).

**Structure-Perimetric Function Relationship in OMD**

**FIGURE 3** shows examples of OCT images in the three perimetric groups. There were differences in the extent or severity of the outer retinal defects. For instance, the eyes in the central scotoma and other scotomata groups showed abnormalities in the IZ, EZ, and external limiting membrane (ELM). In contrast, the foveal structure in the no scotoma group was relatively preserved and did not involve the ELM. **Table 3** shows the SD-OCT phenotypes in the three perimetric groups. There was a significant association of the perimetric findings with a severe phenotype \( (P < 0.001) \). Additionally, the frequencies of ELM involvement (i.e. indistinguishable ELM line from the EZ; yellow arrowheads in Fig. 3) were significantly different among the three groups \( (P < 0.001) \). **Table 3** also presents the findings obtained from other modalities in the perimetric groups. The presence of a hyperautofluorescence spot within normal foveal hypautofluorescence on FAF (arrowheads in Figs. 1E, 1F) was significantly different among the three perimetric groups \( (P = 0.038 \) by Fisher’s exact test). Taken together, the perimetric findings showed significant associations with structural changes.
Table 2. Clinical and Genetic Characteristics of the Three Perimetric Groups With Occult Macular Dystrophy

| Characteristics                     | Central Scotoma (n = 54) | Other Scotomata (n = 14) | No Scotoma (n = 8) | P Value |
|-------------------------------------|--------------------------|--------------------------|--------------------|---------|
| Age, y                              | 45.8 ± 17.6 (17–79)      | 68.0 ± 16.3 (27–86)      | 56.0 ± 11.8 (39–68) | <0.001  |
| Sex, male:female                    | 36 (66.7%):18 (33.3%)    | 6 (42.9%):8 (57.1%)      | 4 (50%):4 (50%)    | 0.200   |
| Age of onset, y                     | 24.0 ± 15.0 (2–60)       | 53.4 ± 16.5 (14–73)      | 45.0 ± 16.2 (22–62) | <0.001  |
| Disease duration, y                 | 21.9 ± 14.4 (5–65)       | 14.6 ± 7.9 (5–28)        | 11.7 ± 4.6 (6–16)  | 0.045   |
| Best-corrected visual acuity, logMAR| 0.666 ± 0.254 (0.15–1.22)| 0.369 ± 0.375 (–0.08–1.00)| 0.094 ± 0.199 (–0.08–0.40)| <0.001  |
| Symptomatic (%)                     | 54 (100%)                | 12 (85.7%)               | 4 (50%)            | <0.001  |
| p.R45W as pathogenic variants (%)   | 39 (72.2%)               | 5 (35.7%)                | 2 (25%)            | 0.004   |
| Mean deviation, dB                  |                          |                          |                    |         |
| 10-2                                | –2.35 ± 1.93 (–6.33–0.09)| –4.44 ± 4.79 (–11.25–0.91)| –0.50 ± 1.00 (–2.81–0.46)| 0.032   |
| 30-2                                | –2.97 ± 2.56 (–11.22 to –0.35)| –3.68 ± 2.35 (–6.03 to –0.63)| N/A           | 0.498   |
| Pattern standard deviation, dB      |                          |                          |                    |         |
| 10-2                                | 2.05 ± 0.57 (1.46–3.13)  | 3.80 ± 3.51 (1.17–8.73)  | 1.14 ± 0.13 (0.97–1.38)| 0.013   |
| 30-2                                | 3.84 ± 1.77 (2.07–9.96)  | 3.24 ± 0.86 (2.31–5.06)  | N/A               | 0.368   |
| Degree                              | 0 degrees to 5 degrees (n = 26, 48.1%), 0 degrees to 10 degrees (n = 23, 42.6%), 0 degrees to 20 degrees (n = 5, 9.3%) | 5 degrees to 15 degrees (n = 6, 46.2%), 0 degrees to 20 degrees (n = 5, 38.5%), 0 degrees to 10 degrees (n = 2, 15.4%) | N/A, N/A |   |

N/A, not applicable.

Figure 3. Structural phenotypes based on photoreceptor status and visual function (global indices in visual field results and best-corrected visual acuities) in the three perimetric groups (A: central scotoma, B: other scotomata, and C: no scotoma). Yellow arrowheads indicate the external limiting membrane (ELM) involvement, indistinguishable ELM line from the ellipsoid zone (EZ). White arrowheads denote normally discernible ELM line from the EZ. BCVA, best-corrected visual acuity; OCT, optical coherence tomography; VF, visual fields; mfERG, multifocal electroretinogram.

Association of Perimetric Features With Symptoms or Other Functional Parameters

Table 2 also shows the frequency of symptomatic eyes among the perimetric groups. All the eyes in the central scotoma group and most eyes (85.7%) in the other scotomata group were symptomatic, whereas 50% of the OMD eyes without any scotoma were symptomatic. The difference in frequencies among the groups was statistically significant (P < 0.001).

There were no significant correlations of BCVA with MD or PSD in the HVF 30-2 or 10-2 test (all P > 0.05), as demonstrated in Supplementary Figure S2. The associations between the perimetric and electrophysiological
(mfERG) findings are presented in Table 3. Central scotoma was significantly associated with homogeneous central/paracentral dysfunction on mfERG (81.6%), whereas the other groups were more likely to have paracentral dysfunction with relatively preserved central/peripheral function (6.1% in the central scotoma groups vs. 33.3% and 37.5% in the other scotomata and no scotoma groups, respectively). The mfERG abnormalities (100%) were noted more frequently than perimetric abnormalities (89.5%), and six (12.2%) and two (16.7%) eyes in the central scotoma and other scotoma groups, respectively, showed widespread dysfunction over the whole area tested on mfERG. Furthermore, all eight eyes without any scotoma showed mfERG abnormalities, in which retinal dysfunction on mfERG was more extensive or sensitive than visual field defects.

**DISCUSSION**

Our study first described the perimetric findings in a large cohort of patients with OMD caused by pathogenic RPE65 variants (Miyake disease). The relationship between the perimetric and structural findings and between the perimetric groups and genotypes was studied. Scotoma, which is the main subjective functional parameter in OMD, was significantly associated with the extent of outer retinal structural damage. Central scotoma was observed in patients with longer disease duration, whereas identification of visual symptoms can occur earlier than scotoma detection, and preceding objective functional damages were identified in some cases. Accordingly, our results highlight the role of visual field examination as a useful method for assessing functional severity and disease stage.

Patients with OMD typically show bilateral central scotoma on standard automated perimetry, which was also confirmed by findings from pointwise frequency maps of scotoma. This finding is compatible with mfERG findings, central macular dysfunction in most patients, and paracentral dysfunction or widespread dysfunction in a minority of patients. However, approximately one-third of the patients in our study showed other patterns of scotoma, which were not suggestive of macular dystrophy, or even no scotoma. The age of onset was earlier and disease duration (between age of onset and that at the examination) was significantly longer in the patient group with central scotoma than the other groups. This finding supports a hypothesis that visual field defects of OMD may not be “typical” in earlier stages and that the central scotoma might develop and progress in the later years. This novel finding in the visual field helps the interpretation of disease severity and supports the usefulness of multimodal clinical examinations for OMD. Specifically, electrophysiological assessments can be particularly helpful in milder cases, whereas visual field testing may be useful for assessing functional damage/progression in later stages.

The visual field test is clinically important as a functional test in terms of the assessment of the severity and location of visual impairment. Our finding of an association between perimetric findings and functional and structural parameters suggests that perimetric findings can predict, to some degree, the other structural or functional findings, although these tests are complementary. In particular, the eyes with central scotoma had structural abnormalities involving the ELM, in addition to the EZ and IZ, and were more likely to be accompanied by worse visual acuities; therefore, those with central scotoma can be considered severe OMD. Thus, the visual field test can also provide a basis for the classification of the severity of OMD.

Photopic or scotopic perimetry is important as a psychophysical test in terms of the assessment of the decrease of sensitivity of the cone or rod system in the macula. Our tests consisted of automated photopic perimetry using commercial perimetric devices, in which rod sensitivity could not be evaluated. However, Miyake et al. reported a loss of cone sensitivity in the macula of all 12 patients with OMD detected by light-adapted perimetry and normal rod sensitivity in 6 (6/12, 50.0%), borderline sensitivity in 3 (5/12, 25.0%), and abnormal sensitivity in 3 (5/12, 25.0%) detected by dark-adapted perimetry. These important findings indicate the impaired macular cone system sensitivity and/or variable macular rod system sensitivity. Our results showing variable patterns of scotoma but the dominance of the central scotoma pattern may be in line with loss of macular cone sensitivity in the cohort published in 2004, although direct comparison is difficult between the previous report in 2004 and our current study due to the different methods using different equipment. It would be intriguing to investigate how preserved/residual rod function is associated with macular rod sensitivity in OMD, with a hallmark of confined cone system dysfunction. However, we could not comment on rod sensitivity in patients with OMD from our results, which requires future studies to elucidate the overall macular functions in the patients.

Functional testing, including objective (mfERG) and subjective (visual fields) tests, showed different advantages in the diagnosis and monitoring of OMD. In both our
previous report on mfERG functional phenotypes and the present study, all the included patients showed mfERG abnormalities, whereas 10.5% of patients showed no abnormality on visual field tests, indicating that mfERG is more sensitive for the detection of functional abnormalities than visual field tests in patients with OMD. Some asymptomatic patients with normal BCVA showed extensive mfERG abnormalities over the macula (see Figs. 1B, 1D); nevertheless, these patients had normal or near-normal perimetric results. Thus, given the advantages of mfERG for detection of cases with normal or near-normal perimetric results, the referral of candidate patients to specialists for clinical diagnosis can be facilitated by mfERG.

However, the advantage of the visual field test is its wide availability in ophthalmology clinics whereas it is sometimes difficult to record mfERG at the local clinic, given the limited access to electrophysiological facilities. The test is also less expensive and time-consuming than other functional tests, including full-field and multifocal ERG. Abnormalities on the visual field test can be more easily interpreted and more familiar to ophthalmologists than those on mfERG and focal macular ERG. Accordingly, this method may be more widely used as an important functional test for patients with OMD. Our results showed that the perimetric parameters varied among the patients with OMD. From the structure-function correlation found in our study as well as in our previous reports, the extent of retinal dysfunction or severity can differ in OMD. The structural and functional phenotypes varied according to the specific genetic condition. Particularly, the pathogenic variant p.R45W (hot spot 1) was significantly associated with central scotoma, compared to other pathogenic variants in hot spot 2 (amino acids 1196–1201). However, the variable disease durations in our patients (and thus the varying degree of progression) and individual and inter-visit variabilities inherent to subjective tests may also lead to the variable results, requiring careful interpretation on the genotype-phenotype association.

Based on these results, our study provides a basis for the clinical utility of automated perimetry in patients with OMD. For diagnosis, the visual field test can be performed to document decreased central visual function, and the presence of bilateral central scotoma can suggest OMD if structural findings (i.e. characteristic photoreceptor changes on the macular OCT in both eyes without any fundus abnormality) are compatible with the disease. Specifically, the 10-2 test, with more test locations on the central vision, may be useful for the sensitive detection of central scotoma, which is confined to the central 10 degrees in most of our cases. Even in those with other scotomata (e.g. paracentral scotoma), VF abnormalities might be detected by the 10-2 test, as all the other types of scotomas included the scotoma points within the central 10 degrees. Although the visual field test results are not suggestive of OMD, other functional tests, such as mfERG, may also confirm the diagnosis. However, repeated visual field tests are desirable for ruling out random errors if characteristic VF findings (e.g. central scotoma) are not obtained in patients with clinically suspected OMD. In addition to its role as a diagnostic tool, the visual field test provides functional information and indicates severe phenotypes and poor visual acuity, particularly in patients with central scotoma. It may also be used as an assessment tool for functional progression; however, as our study was a cross-sectional study, we could not address its role in evaluation of disease progression. This issue should be further elucidated in large, longitudinal studies.

Several limitations of our study require careful consideration when interpreting the results. First, this retrospective study had intrinsic limitations in terms of selection bias. In particular, only patients who underwent genetic screening and had reliable visual field test results were included in this study; this issue needs to be carefully considered when extrapolating our results to other study populations with OMD. Second, different methods for clinical evaluations and genetic screening were used across the participating centers from the different countries. For example, the imaging devices, such as the OCT equipment, were different; therefore, quantitative analyses, including those of retinal thickness, could not be performed, as the measurement may differ across the instruments. Furthermore, the three institutes used two different devices for perimeter, and the test protocols varied from 10-2 to 30-2, which may affect the visual field findings (pattern of scotoma). We separately analyzed the Humphrey 10-2 and 30-2 data for the quantitative analyses in this study to ensure comparability among the data and the quantitative data obtained by the Octopus in a small number of patients were excluded, which might be another source of selection bias. Additionally, although the scotoma patterns on repeated visual field tests were agreeable in the eyes (n = 26) subjected to repeated tests within a time frame of less than 12 months, the variability of the visual field results may be inherent. We noted that the shape and size of the scotoma varied slightly among the visits, although the central scotoma pattern was highly reproducible during the relatively short-term (<12 months) period. Finally, this study was a cross-sectional study; we could not draw any conclusion on the role of the visual field test on disease progression or longitudinal analyses.

In summary, this multicenter study showed prevalence and types of visual field defects in East Asian patients with RPIL1-associated OMD (Miyake disease). The subjective perimetric findings were associated with the objective structural phenotypes, visual and electrophysiological functions, and genotypes. As a widely accessible test, the visual field test is clinically useful for the functional evaluation, diagnosis and classification of OMD.

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This international multicenter study conducted by the East Asia Inherited Retinal Disease Society was performed in three countries: Japan, China, and South Korea. Due to the private information protection laws in each country, some data (such as deep genetic data or detailed clinical data) are not allowed to be shared across borders. The three corresponding authors from each country therefore have full data access separately in their home countries and take responsibility for the integrity of the data and the accuracy of the data analysis. The private information protection laws of China, Korea, and Japan for biospecimens do not allow us to present/publish the genetic/clinical data of patients from their own countries without the corresponding local author taking full responsibility.

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