High-Resolution Photoreceptor Imaging in Idiopathic Macular Telangiectasia Type 2 Using Adaptive Optics Scanning Laser Ophthalmoscopy

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PURPOSE. To study pathologic changes in the photoreceptors in eyes with idiopathic macular telangiectasia (MacTel) type 2 using adaptive optics scanning laser ophthalmoscopy (AO-SLO).

METHODS. Thirteen eyes with nonproliferative MacTel type 2 and 10 normal eyes underwent a full ophthalmologic examination, spectral-domain optical coherence tomography (SD-OCT), and imaging with an original prototype AO-SLO system. All eyes with MacTel type 2 were examined with fluorescein angiography (FA), fundus autofluorescence (FAF), confocal blue reflectance (CBR), and fundus-monitoring microperimetry (MP).

RESULTS. All eyes with MacTel type 2 had ring-like dark areas and/or small patchy regions on AO-SLO images; significantly lower cone density than that of normal eyes in each hemisphere at 0.5 mm from the foveal center; an area with parafoveal reflectance in CBR that was larger than the hyperfluorescence area in FA, the area of increased FAF, the dark areas on AO-SLO, and the area of decreased retinal sensitivity on MP. Dark areas on AO-SLO roughly corresponded to the leakage area in FA, but dark areas were also seen in areas without leakage in 11 eyes, including an eye with the earliest clinical signs of MacTel. Visual acuity and retinal sensitivity correlated with mean cone density 0.5 mm from the center of the fovea.

CONCLUSIONS. In eyes with MacTel type 2, AO-SLO revealed unique dark regions in the cone mosaic and decreased cone density that was associated with decreased vision, even in areas with normal vasculature, which suggests that this feature represents early neuronal changes involved in the pathogenesis of MacTel type 2. (Invest Ophthalmol Vis Sci. 2011;52:5541–5550) DOI:10.1167/iovs.11-7251

Idiopathic macular telangiectasia (MacTel) is a rare condition usually diagnosed in the fifth or sixth decade that causes a slow decline in visual acuity. Gass,1 who originally described this condition as idiopathic juxtapfoveal retinal telangiectasis in 1968, classified it into several types in 19822 and in 1993, he and Blodi,3 revised this classification into three distinct groups. In 2006, Yannuzzi et al.4 proposed a simplified classification of the condition they termed idiopathic macular telangiectasia: idiopathic macular telangiectasia type 1 (aneurysmal telangiectasia) and idiopathic macular telangiectasia type 2 (perifoveal telangiectasia).

Idiopathic MacTel type 2 occurs in both sexes equally and typically manifests bilaterally; however, disease severity may be asymmetric. Mean visual acuity has been reported to be 20/40, but it may decline to 20/200.1–4 MacTel functional impairments typically include parafoveal scotomas, reading difficulties, and metamorphopsia,1–10 and full-thickness macular holes may also occur.11–12

Several clinical signs of MacTel type 2 have been identified using novel imaging techniques such as confocal blue reflectance (CBR),13 macular pigment optical density (MPOD) scanning,11–16 fundus autofluorescence (FAF),17 time-domain optical coherence tomography (TD-OCT), and spectral-domain OCT (SD-OCT), which provides higher-resolution images compared with those provided by TD-OCT.10–25 CBR imaging has showed increased parafoveal reflectance,13 whereas MPOD scanning has showed reduction of MPOD in the macular area,14–16 and FAF imaging has revealed increased FAF signals in the parafoveal area.17 Studies of SD-OCT images have revealed such details as macular structural abnormalities in the outer retina and disruption of the line representing the junction of the photoreceptor inner and outer segments (IS/OS).24–25 However, it is not certain how these abnormalities on images relate to photoreceptor abnormalities or how changes in the photoreceptors relate to other clinical signs.

One reason for continuing uncertainty about these relationships is that OCT and other imaging modalities such as scanning laser ophthalmoscopy (SLO) fail to provide sufficiently detailed images of photoreceptor microstructure, primarily because of aberrations in ocular optics. These aberrations can be compensated for by using imaging systems that incorporate adaptive optics (AO), including a wavefront sensor to measure aberrations in the eye and a deformable mirror or a spatial light modulator to compensate for these aberrations in living eyes.26–30 Adding AO to imaging systems such as a flood-illuminated ophthalmoscope, SLO equipment, or OCT has allowed researchers to identify abnormalities in individual cone photoreceptors in patients with various retinal diseases.31–42

In the study reported here, we used the prototype AO-SLO system we developed to examine the photoreceptors of eyes with nonproliferative MacTel type 2 and compared the pathologic changes we saw with abnormalities on images obtained by other modalities, focusing on cone density, and with abnormalities in these patients’ visual function.
METHODS

All investigations adhered to the tenets of the Declaration of Helsinki, and the study was approved by the institutional review board and the ethics committee at Kyoto University Graduate School of Medicine. The nature of the study and its possible consequences were explained to study candidates, after which written informed consent was obtained from all who participated.

Participants

Participants in this study were 7 patients (13 eyes; 3 men and 4 women; mean age, 66.4 years; range, 58–75 years) with nonproliferative MacTel type 2 but without any other macular abnormality or inherited color blindness, who visited the Kyoto University Hospital, Kyoto, Japan, between September 2008 and May 2010, and 10 healthy volunteers (10 eyes; 5 men and 5 women; mean age, 62.8 years; range, 36–72 years) with no eye diseases. Specific exclusion criteria for eyes with MacTel included neovascular maculopathy (i.e., age-related macular degeneration, polypoidal choroidal vasculopathy, retinal angiomatic proliferation, angioid streaks), pathologic myopia, other causes of secondary macular telangiectasia (i.e., Leber’s disease, retinal vein occlusion, and radiation retinopathy), and any history or signs of retinal surgery, including laser treatment.

Diagnosis and classification of MacTel type 2 were based on the slit-lamp biomicroscopy findings, fundus photographs, and fluorescein angiography (FA) findings, using the grading system proposed by Gass and Blodi.5

All patients and volunteers in this study underwent, at the same visit for each study participant, a comprehensive ophthalmologic examination, including measurements of best-corrected visual acuity (BCVA) and intraocular pressure, indirect ophthalmoscopy, slit-lamp examination, including measurements of best-corrected visual acuity (BCVA) and intraocular pressure, indirect ophthalmoscopy, slit-lamp examination, and color fundus photographs, SD-OCT, and AO-SLO. All patients with MacTel type 2 also underwent, at this same visit, simultaneous FA and indocyanin green angiography (IA) (HRA2; Heidelberg Engineering, Heidelberg, Germany), FAF imaging, CBR imaging, and fundus-monitoring microperimetry (MP) (MP-1; NIDEK, Padova, Italy). The HRA2 with confocal SLO was used for FAF imaging using an excitation wavelength of 488 nm and a barrier filter at 500 nm. The HRA2 was also used to obtain CBR images at a wavelength of 488 nm and an indocyanin green angiography (IA) (HRA2; Heidelberg Engineering, Heidelberg, Germany), FAF imaging, CBR imaging, and fundus-monitoring microperimetry (MP) (MP-1; NIDEK, Padova, Italy). The HRA2 with confocal SLO was used for FAF imaging using an excitation wavelength of 488 nm and a barrier filter at 500 nm. The HRA2 was also used to obtain CBR images at a wavelength of 488 nm. Two independent experienced observers (MY and AH) who used image processing software (ImageJ, developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html) to define the dark regions and AH) who used image processing software (ImageJ, developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html) to define the dark regions and to link each high-resolution, high-magnification SLO image to its exact site of origin on the wide-field retinal images. Because it is confocal, our AO-SLO system allows us to create high-contrast en face images, in any plane, that show individual cone photoreceptor cells, and it also enables recording of real-time videos of blood flow in the vessels.

AO-SLO Images: Cone Mosaic Features

In each eye, AO-SLO images were obtained at multiple locations in the macula. AO-SLO imaging was performed by shifting the focus from the retinal nerve fiber layer to the retinal pigmented epithelium (RPE) and by recording images that showed the cone mosaic. Then, offline, a montage of AO-SLO images was created by selecting the area of interest and generating each image to be included in the montage from a single frame, without averaging. How well each montage corresponded to the area of interest was verified by comparing the AO-SLO image with the wide-field images for that eye.

We next applied the automated cone labeling process of Li and Roorda, which uses an algorithm implemented in MATLAB (The MathWorks Inc., Natick, MA) and a function from the MATLAB Image Processing Toolbox. We manually corrected the results of automated cone labeling on any images for which the algorithm failed to identify the cones, as follows: two independent experienced observers examined each image after automated cone labeling and, if cones were visible but had not been labeled, the observer manually labeled the areas where cones were visible and entered this area into the computer software.

We estimated cone density in areas 0.5 and 1.0 mm from the center of the fovea by instructing the computer software program to divide the number of cones in each area by the size of the area. These distances from the foveal center were selected because the system does not clearly show individual cones within the central fovea, a limitation that has been reported for similar systems.26–42 but does show cones clearly >0.2 mm from the center. To obtain accurate lengths of scans, we corrected the magnification effect in each eye by using the adjusted axial length method devised by Bennett et al.44

To quantify the extent of dark regions in AO-SLO images, each image was examined by two independent experienced observers (MY and AH) who used image processing software (ImageJ), developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html) to define the dark regions and to measure their areas. The area in each eye was taken to be the mean of the areas measured by the two observers.

SD-OCT: Photoreceptor Layer Features and Retinal Thickness Measurements

SD-OCT examinations were performed in all eyes by use of a dual-beam confocal scanning system (Spectralis HRA + OCT; Heidelberg Engineering, Dossenheim, Germany). This image-alignment spectral-domain system has built-in software to calculate retinal thickness, and we used this function to measure the average thickness of the retina on serial B-scan images in each of the sectors identified in the Early Treatment of Diabetic Retinopathy Study (ETDRS).53 The lines delineating the sectors were automatically drawn by the software. After the software had generated boundaries between segments, an experienced observer checked these boundaries visually and corrected them manually if the software had inaccurately interpreted the boundary stemming from structural abnormalities.
The image-processing program (specifically the plot profile function of ImageJ) was used to compare the wide-field SLO images obtained by SD-OCT with high-resolution, high-magnification images obtained using the AO-SLO system. We used this comparison to evaluate the integrity of the line representing the junction of the photoreceptor IS/OS. Reflectivity of this line was measured in a ‘slab’ that was 6 pixels thick and 40 μm deep, starting 20 μm above the RPE and continuing through the IS/OS. Disruption of the IS/OS was defined as a decrease in reflectivity of the IS/OS line on a gray-scale image to 2SDs below the reflectivity of the IS/OS in the unaffected peripheral macula.46

MP: Retinal Sensitivity Measurements

We used fundus-monitoring MP to measure retinal sensitivity. The MP software (MP-1; NIDEK) can be set to automatically track fundus movements and evaluate every acquired frame for shifts in the directions of the x- and y-axes of the fundus with respect to a reference image obtained by an infrared camera at the beginning of the examination.

We used a 4–2 staircase strategy with Goldmann size III stimulus against a white background, with illumination of 1.27 cd/m², to examine 55 stimulus locations covering the central 20°. The differential luminance, defined as the difference between stimulus luminance and background luminance, was 127 cd/m² at 0 decibel (dB) stimulation, and the maximum stimulus attenuation was 20 dB. The duration of the stimulus was 200 ms.

Statistical Analyses

BCVA measured using the Landolt chart was expressed as the Snellen equivalent or the logarithm of minimal angle of resolution (logMAR).

We compared ages for normal eyes and eyes with MacTel using the Mann–Whitney U test. We used a t-test to compare continuous data such as refractive error and cone density for normal eyes and eyes with MacTel. For comparisons of numbers of eyes with various characteristics (e.g., sex), we used Fisher’s exact test. We compared the area with abnormal findings on FA, CBR, or AO-SLO using the Tukey-Kramer test. We calculated the Pearson product-moment correlation coefficient (r) to determine associations between mean cone density and logMAR visual acuity or retinal sensitivity 0.5 mm from the center of the fovea. We calculated the Spearman rank correlation coefficient to determine associations between mean cone density and retinal sensitivity 1.0 mm from the center of the fovea and to determine associations between retinal thickness and retinal sensitivity.

All statistical evaluations were performed using a statistics software program (SPSS17; SPSS Inc., Chicago, IL). A value of P < 0.05 was considered to be statistically significant.

RESULTS

The groups of patients (3 men, 4 women) and volunteers (5 men, 5 women) in this study were statistically not different in sex distribution (P = 0.581, Fisher’s exact test); age (66.4 ± 6.6 years; range: 58 to 75 years for patients; 62.8 ± 10.2 years; range: 59 to 69 years for volunteers; P = 0.536, Mann–Whitney U test); or spherical equivalent of refractive error (0.59 ± 1.46D; range: −2.0 to 2.8D in patients, 0.55 ± 1.39D; range: −0.8 to 3.5D in volunteers; P = 0.794, t-test). The mean logMAR visual acuity was 0.12 in eyes with MacTel type 2. Based on clinical stages proposed by Gass and Bland,1 eye was classified as stage 1, 3 eyes as stage 2, 5 eyes as stage 3, and 4 eyes as stage 4 (Table 1).

Regarding cone density, as Table 2 shows, both in normal eyes and in eyes with MacTel, cone density decreased with increasing distance from the center of the fovea; however, in eyes with MacTel compared with normal eyes, cone density was significantly lower in all areas 0.5 mm from the central fovea. Cone densities were also significantly lower in eyes with MacTel versus normal eyes 1.0 mm from the foveal center in the upper hemisphere (P = 0.012, t-test) and in the temporal hemisphere (P = 0.091, t-test).

With respect to imaging results, in normal eyes, AO-SLO images showed a regular cone mosaic pattern, whereas in eyes with MacTel type 2, AO-SLO images showed peculiar ring-like dark regions with surrounding small patches in the cone mosaic (Fig. 1, stage 2; Fig. 2, stage 3; Fig. 3, stage 4). The eye in this study with stage 1 MacTel type 2 showed only small patchy dark regions (Fig. 4).

In eyes with MacTel type 2, FA showed parfoveal leakage, mainly in the temporal hemisphere, in 12 of 13 eyes (92%). Also, the FAF signal was increased in all eyes (100%); CBR imaging showed increased parfoveal ring-like (9 eyes), or evenly distributed (4 eyes), reflectance in all eyes (100%); and AO-SLO showed foveal and parfoveal dark regions in all eyes (100%) (Table 1). In all eyes the area of increased parfoveal reflectance in CBR was larger than (1) the area of hyperfluorescence in FA, (2) the area of increased FAF, (3) the dark regions in AO-SLO (Table 1), and (4) the area of decreased retinal sensitivity on MP (Figs. 1–4).

The mean area with parfoveal reflectance in CBR (5.60 ± 0.90 mm²) was larger than the mean hyperfluorescence area in FA (1.54 ± 0.94 mm², P < 0.001, Tukey–Kramer test) or the mean cone alteration area in AO-SLO (1.69 ± 0.89 mm², P < 0.001, Tukey–Kramer test).

Table 1. Clinical Findings in 13 Eyes with Idiopathic MacTel Type 2 by Imaging Modality

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Eye</th>
<th>Visual Acuity</th>
<th>Stage</th>
<th>FAF Categorya</th>
<th>FA Leakage Area (mm²)</th>
<th>CBR High Reflectance Area (mm²)</th>
<th>AO-SLO Dark Regions (mm²)</th>
</tr>
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<tr>
<td>1</td>
<td>72</td>
<td>F</td>
<td>R</td>
<td>20/20</td>
<td>3</td>
<td>3</td>
<td>1.13</td>
<td>4.63</td>
<td>1.31</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>R</td>
<td>20/25</td>
<td>2</td>
<td>3</td>
<td>0.79</td>
<td>4.85</td>
<td>1.05</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>R</td>
<td>20/32</td>
<td>3</td>
<td>5</td>
<td>0.66</td>
<td>5.59</td>
<td>0.92</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>F</td>
<td>R</td>
<td>20/32</td>
<td>3</td>
<td>4</td>
<td>2.09</td>
<td>5.58</td>
<td>2.10</td>
</tr>
<tr>
<td>5†</td>
<td>67</td>
<td>M</td>
<td>R</td>
<td>20/16</td>
<td>2</td>
<td>3</td>
<td>2.72</td>
<td>6.13</td>
<td>2.12</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>F</td>
<td>R</td>
<td>20/30</td>
<td>3</td>
<td>2</td>
<td>2.19</td>
<td>5.61</td>
<td>2.05</td>
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<tr>
<td>7</td>
<td>75</td>
<td>F</td>
<td>R</td>
<td>20/42</td>
<td>4</td>
<td>4</td>
<td>2.91</td>
<td>6.07</td>
<td>3.31</td>
</tr>
</tbody>
</table>

a Category proposed by Wong et al.17
† This patient’s left eye was excluded as a result of choroidal neovascularization (stage 5).
Interobserver reproducibility of the measurement of abnormal regions in each image was assessed by calculating the interobserver intraclass correlation coefficient (ICC); ICCs were 0.961, 0.975, and 0.953 for the measurement of FA leakage area, CBR reflectance area, and AO-SLO dark regions, respectively.

### TABLE 2. Cone Density in Normal Eyes and Eyes with Idiopathic MacTel Type 2

<table>
<thead>
<tr>
<th>Distance from Central Fovea/Hemisphere</th>
<th>Normal Eyes (10 Eyes of 10 Volunteers) (cones/mm²)</th>
<th>Eyes with MacTel (13 Eyes of 7 Patients) (cones/mm²)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>31.987 ± 10.329</td>
<td>17.102 ± 9.969</td>
<td>0.002</td>
</tr>
<tr>
<td>Nasal</td>
<td>31.655 ± 10.177</td>
<td>19.204 ± 10.871</td>
<td>0.011</td>
</tr>
<tr>
<td>Lower</td>
<td>30.079 ± 10.729</td>
<td>18.721 ± 10.428</td>
<td>0.018</td>
</tr>
<tr>
<td>Temporal</td>
<td>31.016 ± 10.286</td>
<td>9.815 ± 10.817</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.0 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>14.972 ± 2.209</td>
<td>11.826 ± 3.048</td>
<td>0.012</td>
</tr>
<tr>
<td>Nasal</td>
<td>14.867 ± 2.136</td>
<td>13.554 ± 1.851</td>
<td>0.150</td>
</tr>
<tr>
<td>Lower</td>
<td>14.112 ± 2.950</td>
<td>12.672 ± 3.071</td>
<td>0.270</td>
</tr>
<tr>
<td>Temporal</td>
<td>14.892 ± 2.841</td>
<td>7.275 ± 6.310</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* t-test.

![Figure 1](https://iovs.arvojournals.org/) Images of the left eye of a 58-year-old woman with type 2 idiopathic MacTel (stage 2) with a Snellen equivalent BCVA of 20/20. (A) The fundus shows crystalline deposits and graying of the macula of the retina. (B) A late-phase FA image showing parafoveal telangiectasis. Leakage is observed superior and temporal to the fovea but none to the inferior of and less on the nasal side of the fovea (arrow). (C) A FAI image showing slightly increased levels of FAF signaling in the fovea. (D) A CBR image showing a ring-like area of increased parafoveal reflectance and crystalline deposits. (E) A fundus-related MP image showing a parafoveal scotoma temporal to the fovea. (F) An infrared image, with green arrows indicating the size of the double-headed arrows in (G) and (H). (G, H) SD-OCT images. (G) A horizontal-line scan through the center of the fovea, taken in the direction of the horizontal arrow in (F), revealing hyperreflective spots in the outer nuclear layer (arrowheads). The line representing the junction between the inner and outer photoreceptor segments (IS/OS) between the blue arrows is irregular on the temporal side of the fovea. (H) A vertical line scan through the center of the fovea, in the direction of the vertical arrow in (F), demonstrating a small flat cavity in the fovea (arrowhead) and an irregular IS/OS on the superior side of the fovea (between the blue arrows). Scale bar, 1000 µm. (I) AO-SLO images of the area indicated by a white box in (F) showing ringlike dark regions (yellow arrows), surrounded by small dark patches (red arrows). Dark regions are predominant superior and temporal to the fovea where there is IS/OS irregularity (G and H), hyperfluorescence (B), and decreased retinal sensitivity (E). The areas where these features appear are smaller than the area of increased reflectance on the CBR image (D). The asterisk indicates the fixation point. Middle: High-magnification views of the areas outlined by the large white box (left) and yellow box (right). Bottom: High-magnification views of the areas outlined by the white boxes (a: left, b: middle, c: right).
Dark regions in the AO-SLO images appeared to be ring-like and temporally shifted, roughly corresponding to the leakage area in FA (Figs. 2 and 3); however, small patchy dark regions were also seen in areas without FA abnormalities in 11 eyes (85%) (Figs. 1 and 2), including an eye with the earliest clinical signs of MacTel and minimal FA leakage in the macula (Fig. 4).

Among eyes with MacTel type 2, cone density was lower in those with stage 3 or stage 4 versus stage 1 or stage 2 MacTel, and the difference was significant for the nasal hemisphere 0.5 mm from the fovea, and the temporal hemisphere 1.0 mm from the fovea (Table 3) ($P = 0.001$, t-test).

Comparison of AO-SLO and SD-OCT images in eyes with MacTel type 2 showed that dark regions in the AO-SLO images corresponded to areas in the SD-OCT images where the line representing the IS/OS was disrupted (Figs. 1–3). In eyes with later-stage MacTel, the dark regions on AO-SLO images corresponded to loss of the outer photoreceptor layer on SD-OCT images (Figs. 2 and 3).

In eyes with MacTel type 2, the greater decrease in cone density 0.5 mm from the fovea was related to disruption in the line representing the IS/OS on SD-OCT images (Table 4).

The greater decrease in retinal sensitivity 0.5 mm from the center of the fovea was related to SD-OCT findings of disruption in the line representing the IS/OS in the nasal, lower, and temporal hemispheres (Table 5).

In eyes with MacTel type 2, higher visual acuity correlated with greater mean cone density 0.5 mm from the center of the fovea ($P = 0.003$, $r^2 = 0.570$) (Fig. 5). In addition, higher retinal sensitivity correlated with greater cone density, both 0.5 mm ($P < 0.001$, $r^2 = 0.634$) and 1.0 mm ($P < 0.001$, $r^2 = 0.434$) from the center of the fovea.

However, mean retinal thickness in each ETDRS sector measured on SD-OCT images did not correlate with mean retinal sensitivity (Table 6).
pigment) that may precede typical clinical and angiographic indicators of early anatomic changes (decreased density of macular photoreceptors) have been identified using novel noninvasive imaging techniques such as MPOD obtained using a confocal SLO, including inner lamellar cavities, disruption of the IS/OS, thinning of the central and parafoveal retina, highly reflective areas consistent with intraretinal pooling of dye, outer retinal defects (red arrowheads), and proliferation of pigment (arrow) that masks the underlying retinal structure. The IS/OS is disrupted temporal to the fovea (between the blue arrows). A vertical line scan through the center of the fovea, taken in the direction of the horizontal arrow in (F), revealing an inner retinal cavity (arrowheads), outer retinal defects (red arrowheads), and proliferation of pigment (arrow) that masks the underlying retinal structure. The IS/OS is disrupted temporal to the fovea (between the blue arrows). A horizontal line scan through the center of the fovea, taken in the direction of the vertical arrow in (F). The IS/OS is widely disrupted in the fovea and parafovea (between the blue arrows). Scale bar, 1000 μm. (I) AO-SLO images of the area indicated by the white box in (F) and the double-headed arrows in (G) and (H) showing ring-like dark regions (within arrows). Red arrowheads indicate the shadow in areas displaying pigment proliferation. Large dark regions, mainly superior and temporal to the fovea and corresponding to the areas of hyperfluorescence (B), increased FAF (C), IS/OS disruption (G, H), and decreased retinal sensitivity (E) are visible. The areas wherein these features appear on various images are smaller than the area of increased reflectance on the CBR image (B). The asterisk indicates the fixation point. Bottom: High-magnification views of the areas outlined by the white boxes (a: left, b: middle, c: right).

**DISCUSSION**

MacTel type 2 was initially characterized by biomicroscopic clinical observations and FA results. Recently, other characteristics have been identified using novel noninvasive imaging techniques such as MPOD obtained using a confocal SLO, which showed reduction in MPOD in the macular area but preservation at 5° to 7° eccentricity. CBR imaging showed a parafoveal area of increased reflectance that corresponded to an area of reduced MPOD. Both the area of reduced MPOD and the area of increased CBR were larger than the area of FA abnormalities. FAF results that show loss of central masking indicate early anatomic changes (decreased density of macular pigment) that may precede typical clinical and angiographic changes.

Studies using OCT images obtained in eyes with MacTel type 2 have revealed structural abnormalities in these eyes, including inner and outer lamellar cavities, disruption of the line representing the IS/OS, thinning of the central and parafoveal retina, highly reflective areas consistent with intraretinal pigment migration, and outer retinal hyperreflective spots. The study reported here, in addition to confirming the presence of MacTel type 2 features such as increased parafoveal reflectance in CBR images and increased signal in FAF images, is the first to report structural abnormalities in the photoreceptors and correlation between this anatomic finding and visual function in eyes with MacTel type 2.

Specifically, using AO-SLO, we saw dark regions in the cone mosaic in eyes with MacTel type 2, and we did not see such areas in any normal eyes. Dark regions were differentiated from the shadows of blood vessels or intraretinal pigment proliferation of the RPE (Fig. 3) by comparing AO-SLO images and wide-field SLO images or fundus photographs. The presence of an inner lamellar cavity or crystalline deposits may affect the amount of light reflected from the deeper layers. However, we found that the cone mosaic was visible even in areas with an inner lamellar cavity or crystalline deposits as detected on SD-OCT or fundus photographs (Figs. 1–3). Decreased transparency of the retina seems to have little or no effect on light reflected from the deeper layers; we believe this is because SD-OCT, which uses a light source with a wavelength (840 nm) similar to that of our AO-SLO system, showed no shadows in the photoreceptor layer in the gray area of the retina in fundus photographs. Moreover, the dark regions we saw on AO-SLO images corresponded to areas of disruption in the IS/OS on SD-OCT images. Thus, it appears reasonable to suppose that the dark regions visible on AO-SLO images represent abnormal-
ities at the level of the photoreceptors, possibly loss of the cone photoreceptor cells.

We also found that the dark regions on AO-SLO images corresponded roughly to the areas of leakage on FA; however, small patchy dark regions were seen even in areas without angiographic abnormalities. This finding is similar to the findings of disruption of the IS/OS, although retinal thickness did not correlate with retinal sensitivity, which is consistent with morphologic alterations in eyes with MacTel type 2.5–9 Charbel Issa and colleagues6 reported that macular sensitivity significantly decreased temporal to the fovea, and light sensitivity deteriorates incrementally in eyes with more severe stages of MacTel. Maruko et al.7 reported a reduction in the retinal sensitivity thresholds temporal to the fovea, particularly in areas where there were breaks in the line representing the IS/OS and the area where a vein makes a right angle, corresponding to the point where the outer retinal layer disappears. In the present study, retinal sensitivity was related to SD-OCT findings of disruption of the IS/OS, although retinal thickness did not correlate with retinal sensitivity, which is consistent with a study using TD-OCT and MP.6 Possibly, mean retinal thickness does not fully reflect the retinal status because retinal atrophic changes such as inner and outer retinal cavities may be masked in measuring retinal thickness. Therefore, photoreceptor disruptions, rather than retinal thickness, may be closely related to visual function in MacTel type 2. In addition, our AO-SLO imaging study yielded quantitative differences in eyes with MacTel, specifically decreased parafoveal cone density in the temporal hemisphere in eyes with MacTel type 2.

Functional impairment has been shown to be correlated with morphologic alterations in eyes with MacTel type 2.5–9 Damage secondary to vascular abnormalities, but rather earlier neuronal changes involved in the pathogenesis of MacTel type 2.

<table>
<thead>
<tr>
<th>Distance from Central Fovea</th>
<th>Stage 1 or 2 (4 Eyes of 4 Patients) (cones/mm²)</th>
<th>Stage 3 or 4 (9 Eyes of 6 Patients) (cones/mm²)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mm</td>
<td>20,863 ± 7,416</td>
<td>15,431 ± 10,874</td>
<td>0.388</td>
</tr>
<tr>
<td>Upper</td>
<td>28,208 ± 6,529</td>
<td>15,203 ± 10,138</td>
<td>0.040</td>
</tr>
<tr>
<td>Nasal</td>
<td>23,494 ± 7,577</td>
<td>16,600 ± 11,187</td>
<td>0.290</td>
</tr>
<tr>
<td>Lower</td>
<td>14,112 ± 11,062</td>
<td>7,903 ± 10,785</td>
<td>0.362</td>
</tr>
<tr>
<td>Temporal</td>
<td>15,056 ± 11,062</td>
<td>12,863 ± 10,785</td>
<td>0.404</td>
</tr>
<tr>
<td>1.0 mm</td>
<td>13,182 ± 1,510</td>
<td>11,223 ± 3,429</td>
<td>0.305</td>
</tr>
<tr>
<td>Upper</td>
<td>13,305 ± 1,704</td>
<td>13,665 ± 2,002</td>
<td>0.761</td>
</tr>
<tr>
<td>Nasal</td>
<td>14,383 ± 878</td>
<td>11,912 ± 3,428</td>
<td>0.192</td>
</tr>
<tr>
<td>Lower</td>
<td>13,920 ± 1,776</td>
<td>4,366 ± 5,257</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* t-test.
decreased cone density (anatomic abnormalities in the photoreceptor cell layer visible on AO-SLO images) is correlated with worse visual acuity and retinal sensitivity.

In the present study, we further compared AO-SLO findings with SD-OCT findings in eyes with MacTel type 2. We found correlation between SD-OCT evidence of an interrupted IS/OS line and AO-SLO findings of disruption of the cone mosaic pattern, indicated by dark regions. In eyes with MacTel type 2, a greater decrease in cone density was related to a larger area of disruption, in each direction, in the line representing the IS/OS in SD-OCT images. These results are consistent with the results of previous studies of eyes with macular microholes or resolved central serous chorioretinopathy, in which the dark area seen in the AO images corresponded with the areas where the line representing the IS/OS in the cone outer segment tip was disrupted in corresponding SD-OCT images. We believe our inability to detect small patchy dark regions seen in AO-SLO by SD-OCT is attributed to the small dark regions we saw (using AO-SLO), which have a lateral resolution of 2 μm and were approximately 5 to 20 μm, whereas the lateral resolution of commercially available SD-OCT systems, which do not have AO, is approximately 20 μm.

In our study, the area with increased parafoveal reflectance in CBR images was larger than the area of hyperfluorescence on FA, the area of increased FAF, the area of dark regions in MP, and the area of decreased retinal sensitivity on MP in all eyes with MacTel type 2. Charbel Issa et al. reported that the area of increased CBR and reduced MPOD had the same size and location in eyes with MacTel type 2, suggesting that the density of macular pigment is reduced in areas with increased reflectance on CBR images. They also postulated that the area of increased reflectance on CBR of eyes with MacTel type 2, appears that decreased density of macular pigment contributes to neurosensory atrophy, as suggested by Helb et al. It can also be speculated that Müller cell degeneration would be accompanied by loss of neurons, as suggested by Gaudric et al. Recently, Powner et al. reported that targeted disruption of Müller cell–specific markers in the central macula of a macular model suggested that Müller cell depletion or dysfunction may be a major contributor to the pathologic features in MacTel type 2. Moreover, the area that lacked Müller cells corresponded with the region of depleted macular pigment. Jablonski and Lannaccone reported that a targeted disruption of Müller cell metabolism adversely affected photoreceptor outer segment membrane assembly, causing dysmorphogenesis of nascent outer segments in an animal model. Further histologic study would help to confirm anatomic findings and reveal more about the mechanism of this disease.

Although the lateral resolution of AO-SLO is superior to that of commercially available SD-OCT equipment, AO imaging equipment currently available cannot clearly show individual cone photoreceptors in the foveal center. An additional limitation in our study is that because it is cross-sectional, we cannot state that the dark regions we saw on AO-SLO images in

### Table 4. Mean Cone Density versus Integrity of the Photoreceptor IS/OS Junction 0.5 mm from Central Fovea in Eyes with Idiopathic MacTel Type 2

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Intact IS/OS (cones/mm²)</th>
<th>Disrupted IS/OS (cones/mm²)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper</td>
<td>21,180 ± 8,614 (n = 9)</td>
<td>7,929 ± 6,132 (n = 4)</td>
<td>0.019</td>
</tr>
<tr>
<td>Nasal</td>
<td>24,847 ± 8,528 (n = 8)</td>
<td>10,177 ± 7,860 (n = 5)</td>
<td>0.010</td>
</tr>
<tr>
<td>Lower</td>
<td>22,918 ± 7,300 (n = 10)</td>
<td>4,732 ± 5,578 (n = 3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Temporal</td>
<td>22,385 ± 8,202 (n = 3)</td>
<td>6,042 ± 8,520 (n = 10)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

* t-test.

### Table 5. Mean Retinal Sensitivity versus Integrity of the Photoreceptor IS/OS Junction 0.5 mm from Central Fovea in Eyes with Idiopathic MacTel Type 2

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Intact IS/OS (dB)</th>
<th>Disrupted IS/OS (dB)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper</td>
<td>15.1 ± 1.8 (n = 9)</td>
<td>9.8 ± 7.8 (n = 4)</td>
<td>0.065</td>
</tr>
<tr>
<td>Nasal</td>
<td>16.6 ± 3.2 (n = 8)</td>
<td>10.4 ± 6.6 (n = 5)</td>
<td>0.040</td>
</tr>
<tr>
<td>Lower</td>
<td>15.7 ± 3.2 (n = 10)</td>
<td>8.5 ± 7.2 (n = 3)</td>
<td>0.023</td>
</tr>
<tr>
<td>Temporal</td>
<td>14.7 ± 2.5 (n = 3)</td>
<td>4.3 ± 5.9 (n = 10)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* t-test.

![Figure 5. Correlation of mean cone density in areas superior, nasal, inferior, and temporal to the fovea at 0.5 mm from the center of the fovea with BCVA expressed as the logMAR in 13 eyes with MacTel type 2 (P = 0.003, r² = 0.570).](image-url)
TABLE 6. Retinal Thickness and Retinal Sensitivity in Eyes with Idiopathic MacTel Type 2

<table>
<thead>
<tr>
<th>ETDRS Sector</th>
<th>Mean Retinal Thickness (µm)</th>
<th>Mean Retinal Sensitivity (dB)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center</td>
<td>233.7 ± 15.5</td>
<td>12.4 ± 3.8</td>
<td>0.491</td>
</tr>
<tr>
<td>Upper†</td>
<td>294.7 ± 20.6</td>
<td>15.3 ± 2.3</td>
<td>0.522</td>
</tr>
<tr>
<td>Nasal†</td>
<td>301.2 ± 29.8</td>
<td>18.2 ± 1.2</td>
<td>0.746</td>
</tr>
<tr>
<td>Lower†</td>
<td>295.6 ± 15.5</td>
<td>17.2 ± 2.8</td>
<td>0.469</td>
</tr>
<tr>
<td>Temporal†</td>
<td>288.8 ± 17.3</td>
<td>15.1 ± 4.2</td>
<td>0.125</td>
</tr>
</tbody>
</table>

*p* Spearman’s rank correlation.
† Inner ring (3 mm) of the ETDRS sector.

eyes with MacTel type 2 actually represent cone loss: these dark regions could represent reversible changes in the cones. However, we believe it is likely that the dark regions are related to the pathophysiology of MacTel type 2 because they were spatially associated with loss of the outer photoreceptor layer, because decreased cone density on AO-SLO images was associated with disruption of the line representing the IS/OS, and because cone density was lower in eyes with later stages of MacTel type 2. All these findings indicate that the dark regions on AO-SLO images mainly represent cone loss. We hope to perform longitudinal studies using AO-SLO to confirm this interpretation and to learn more about the involvement of this peculiar feature in the pathogenesis of MacTel type 2, as a possible prelude to better management of this disease.

Acknowledgments

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References


