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IMPAIRMENTS IN CONE PIGMENT REGENERATION AND ABSOLUTE THRESHOLD IN MACULAR TELANGIECTASIA TYPE 2

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Purpose: To test the hypothesis that Müller cell dysfunction in macular telangiectasia type 2 (MacTel) results in delayed cone adaptation kinetics and to assess absolute cone and rod thresholds in this condition.

Methods: Adaptation after an approximate 63.5% full-field cone photopigment bleach was assessed for Goldmann size V (1.7° diameter) 640 nm (red) and 480 nm (blue) targets presented at a retinal locus corresponding to 2° temporal to fixation. The cone time constant of adaptation and absolute cone and rod thresholds were calculated from exponential functions fitted to the resultant dark adaptation curves.

Results: Eighteen eyes with MacTel (from 11 patients) were compared with 19 control eyes (from 16 normal subjects). Cone adaptation kinetics were significantly impaired in MacTel, as was the absolute cone threshold. Final thresholds for blue targets were also significantly elevated in MacTel, consistent with impaired rod absolute threshold. Losses in sensitivity observed in MacTel were consistent with a so-called *d1/2* mechanism (i.e., receptoral) site of sensitivity loss.

Conclusion: In addition to previously documented impairments in rod dark adaptation, MacTel results in a significant elevation in cone thresholds because of pathology at the level of the photoreceptors. The delays in cone adaptation that we found in eyes with MacTel may reflect impairment of the Müller cell–mediated cone-specific visual cycle.

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Macular telangiectasia type 2 (MacTel) is a bilateral disorder of the macula which affects up to one in 2,000 individuals older than 40[1] and which was first described in 1977.[2] It is associated with vascular abnormalities which typically occur in the temporal parafoveal region, with the locus of onset occurring 1° to 2° from the fovea center temporally, but which later encompasses an oval-shaped area of 6° (horizontally) by 5° (vertically), centered on the fovea.[3] The vascular anomalies in MacTel are associated with outer retinal abnormalities on clinical imaging. Early clinical changes include "blunting" of the foveal reflex, a graying of the temporal retina, intraretinal crystals, and low-grade leakage on fundus fluorescein angiography.[3] As the disease progresses, stellate intraretinal retinal pigment epithelium migration and so-called right angle retinal vascular changes (resulting from vascularization of the outer retina) occur. The condition may sometimes be associated with choroidal neovascularization or macular holes. Although MacTel was initially described as a disorder of the macular vasculature, this does not seem to be the primary site of pathology; advanced imaging techniques and histo-

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pathological analysis implicate the early loss of both the macular pigment and the Müller cells.[3]

MacTel is familial; both genome-wide association studies and metabolomic investigations point to an underlying alteration in serine metabolism, with a decrease in serum serine levels of the order of 20%.[4] Murine models of MacTel can be induced with low-serine diets, and such mice demonstrate electroretinographic evidence of aberrant cone function.[4] Histopathological examination of postmortem retinae in MacTel has revealed loss of the Müller cells and photoreceptors.[5] More recently, in vivo imaging of the foveal cones with adaptive optics techniques has elucidated loss of cones/disruption of the cone mosaic, even early in the disease course.[6] Thus, there is significant and mounting evidence to support the hypothesis that the Müller cells are the primary site of pathology in MacTel, with photoreceptor changes occurring subsequently.[3–5] The Müller cells are believed to play a crucial role in sustaining cone-mediated vision under photopic light conditions. Specifically, an accessory and relatively recently described cone-specific visual cycle, distinct from the canonical retinal pigment epithelium-mediated visual cycle, is believed to be mediated by the Müller cells. This is believed to account for the fact that cone dark adaptation kinetics are more rapid than rod kinetics after exposure to "bleaching" light sources.[7]

The functional correlates of the structural changes reported in MacTel include impaired acuity and threshold sensitivity.[3] Although the visual acuity for single letters may be well-preserved, paracentral visual function may be severely damaged; such patients may demonstrate impaired reading ability and deep paracentral scotomata.[8] With the advent of clinical trials exploring treatments for this condition (ClinicalTrials.gov identifiers NCT01354093, NCT01949324, NCT01327911, NCT03071965, NCT00685854, and NCT01205035), establishing in detail the effects of MacTel on visual function is critical. Many clinical trials focus on the best-corrected visual acuity (BCVA) to assess functional outcomes; however, such measures of central spatial resolution are unlikely to reflect the progression of paracentral retinal dysfunction in patients with MacTel. Although microperimetry—a perimetric technique that combines threshold sensitivity testing with clinical imaging—has been mooted as a suitable means of assessing function in patients with MacTel,[8] our previous investigations suggest that this test may be insensitive to small changes in function because the mesopic background luminance level it uses by default results in redundancy of target detection (Figure 1).[9] However, it should also be noted that newer paradigms, such as scotopic microperimetry, may address the issue of rod isolation.[10]

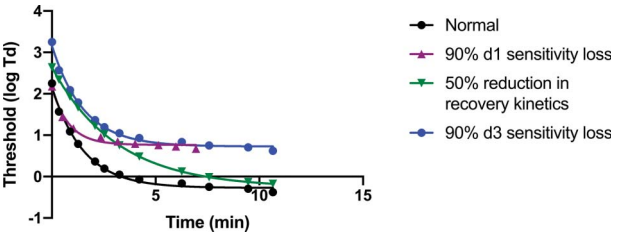

Fig. 1. Normal cone dark adaptation data plotted as log threshold versus time for a 4.6 log Td bleach (black filled circles); 90% d1/2 sensitivity loss/filter effect (purple-filled triangles) determined empirically by adjusting for bleaching intensity and the effects of a filter on stimulus intensity; 90% d3 sensitivity loss (blue-filled circles) and 50% reduction in recovery kinetics (green-filled triangles). See text for details.

We aimed to explore the hypothesis that there is a dysfunction of light adaption in the cone photoreceptors in MacTel. Evidence accrued over the last decade-and-a-half suggests that although the canonical visual cycle of chromophore regeneration is retinal pigment epithelium dependent, this process is slow and possibly more critical for the rods than the cones.[7] As outlined above, there is growing evidence that the Müller cells provide an alternative, faster, pathway of photopigment regeneration in the cones, which facilitates vision under photopic conditions.[7] Although progressive dysfunction of the Müller cells alone might not produce an appreciable effect on detection thresholds measured with perimetry, we hypothesize that Müller cell dysfunction results in delayed cone adaptation kinetics in eyes with MacTel. The only available report of dark adaptation in MacTel did not report dark adaptation kinetics in cones.[11] Previous detailed investigations of psychophysical function in MacTel have described losses in absolute cone and rod threshold for 505 nm (blue–green) 2° circular targets presented in the region of the visual field centered on a corresponding retinal location 5° temporal to the foveal center.[11] The early involvement of Müller cells in MacTel[3]—together with their crucial role in cone photopigment regeneration[7]—suggests that eyes with MacTel will have delayed cone adaptation kinetics.

Materials, Subjects, and Methods

This was a prospective, single-center, cross-sectional study of patients presenting to, or followed-up in, the Medical Retina Unit at Sydney Eye Hospital, Sydney, Australia. Patients were diagnosed with MacTel based on clinical characteristics, optical coherence tomography (OCT) scanning, and fundus fluorescein angiography.

Participants

Subjects with MacTel (18 eyes from 11 patients; age range 47–85 years; mean age 59.7 years) with log of the minimum angle of resolution BCVA ranging from −0.08 to 1.1 (mean 0.32; SI Snellen equivalent $6/5^{-1}$ to 5/60) were classified according to the scheme proposed by Gass and Blodi[12] and were recruited after obtaining written informed consent. Eyes were excluded if patients were unable to maintain steady fixation (one eye excluded: BCVA of included eye −0.08 to 0.46; SI Snellen equivalent $6/5^{-1}$ to $6/19^{+2}$) or if they had previously undergone implantation of a ciliary neurotrophic factor implant (three eyes). Four MacTel participants had diabetes mellitus, although they had no evidence of diabetic retinopathy or any other concurrent ocular conditions. All subjects had clear media: one MacTel and one normal control subject were pseudophakic. Normal controls were recruited by local advertising (19 eyes from n = 16 patients; age range 35–67; mean age 46.4 years). The study was approved by the local research ethics committee (HREC/17/POWH/537SSA18/G/311) and followed the tenets of the Declaration of Helsinki.

Examination and Psychophysical Protocol

All subjects underwent clinical examination, including assessment of best-corrected visual acuity, dilated fundus examination, Heidelberg Spectralis spectral domain OCT (Heidelberg Engineering GmbH), and dark adaptometry. Spectral –domain OCT scans (30° × 25° volume scans) of the macula were inspected for preservation of the photoreceptor layer within the retinal locus examined in dark adaptometry (preserved, partially disrupted, and undiscernible). Dark adaptation testing was conducted with the MonCVOne CR perimeter (MetroVision, Paris, France). The standard protocol for dark adaptation with the device commences with an intense bleaching phase (5 minutes adaptation to a neutral white background at 600 cd/m^2; equivalent to 4.5 log Td and a 63.5% cone bleach)[13] the bleaching light was then extinguished, and sensitivity was determined with Goldmann size V (1.7°) 640 nm (red) and 480 nm (blue) targets centered 2° nasal to fixation (i.e., to the temporal retina within the so-called "MacTel zone")[3] over 30 minutes using a staircase protocol similar to one previously described.[14] In brief, the stimulus was presented for 500 ms at an initial intensity of 318 cd/m^2; its intensity was adjusted in 5 dB steps before and after the first reversal in response; this was modified to a 1 dB step asymmetric staircase thereafter, whereby intensity was only increased after consecutive nonresponses but could be decreased after a single response. During testing, fixation was monitored by an experienced examiner.

Modeling of Dark Adaptation Functions

Cone adaptation functions have been modeled with monophasic exponential[15] as well as biphasic exponential functions[16] (when plotted as log threshold vs. linear time), and rod dark adaptation has been modeled with both monophasic exponential[15,17] and multiple linear functions in normal subjects.[18] The advantage of fitting dark adaptation data with monophasic exponential functions is that it affords an overall comparison of adaptation of the rod and cone systems, respectively, through the generation of key summary variables. Furthermore, fitting of exponential functions provides an adequate empirical description of dark adaptation,[17] and this approach is generally used in the clinical research literature.[11,14,15] Accordingly, we fitted our cone and rod data with monophasic exponential functions of the form:

$$V = V_0 + A \times e^{-t/\tau} \quad (1)$$

where V is threshold, V_0 is final threshold, A is the adaptation constant/span of thresholds (in turn a function of the intensity and duration of the adapting light), t is time in minutes, and τ is the time constant of adaptation. The greater the value for τ, the slower the rate of recovery in sensitivity.

The model outlined in Equation 1 above has the advantage of permitting predictions regarding alterations in the dark adaptation curve according to the site of loss of sensitivity and the kinetics of photopigment regeneration. The equivalent background hypothesis posits that the after effects of light adaptation, or "bleaching," act as an equivalent or "virtual" background, desensitizing the retina.[19] If we invoke this hypothesis and concurrently model sensitivity loss according to the site of retinal pathology (as initially posited by Hood and Greenstein),[20] the effects of retinal pathology on threshold versus intensity functions (and therefore dark adaptation curves) can be modeled. Loss of retinal sensitivity has previously been divided into so-called *d1/2* loss (also known as a "filter effect") and *d3* loss.[20–23] *d1/2* loss is theorized to result from receptoral disease and to act like a "filter." A filter effect is anticipated to result in upward and leftward shift of the dark adaptation curve for submaximal bleaches (modeled in Figure 1 by translation of normative data from Hecht et al[24] adjusted for initial bleach and the effects of a filter on stimulus intensity). *d3* loss, however, is anticipated to manifest as an upward translation of the curve. If, however, the disease

process impairs the kinetics of photopigment recovery, then the initial threshold will be increased and the adaptation curve will take longer to approach the final plateau (see Figure 1 for a graphical demonstration of *d1/2*, *d3* loss, and increases in τ, modeled on the findings of Hecht and colleagues in normal subjects).[24] We hypothesized that MacTel's effects on Müller cell function would delay cone adaptation kinetics and elevate rod and cone final thresholds by a *d1/2* mechanism.

In modeling the effects of reductions in cone photopigment regeneration, we used the calculations derived by Rushton et al:

$$Q_e = I_0 \times t_0 \qquad 2$$

where Q_e is the energy of a flash (in Td/sec) required to bleach the proportion of unbleached photopigment from one to e^{-1}, I_0 is in the intensity of a background which in equilibrium bleaches half of the photopigment, and t is the time constant of regeneration (where t_0 is approximated by τ). Bleaches were calculated according to an equation outlined by Reeves et al,[13] which is based on modeling of empirical data:

$$p = k/\sqrt{I^2 + k^2} \qquad 3$$

where P is the proportion of pigment available at equilibrium, k is a constant equal to $I_0/\sqrt{3}$, and I is the background irradiance in Td.

We assumed dark adaptation curves for a Goldmann size V 640 nm stimulus would be best described by a monophasic exponential decay, consistent with our previous observations of mechanisms contributing to target detection with similar parameters under scotopic conditions/at absolute threshold.[9] 480 nm data were permitted to be fitted with two exponential decay functions (i.e., to allow for a so-called cone-rod break, which was determined by departure from the translated curve fitted to the 640 nm stimulus thresholds). Curve fitting was performed with GraphPad Prism eight; statistical calculations were performed with SPSS (IBM, Armonk, NY), using a linear mixed-effects model, with diagnosis (MacTel vs. normal, Gass–Blodi classification or photoreceptor status within the region tested [normal, absent, or disrupted]) set as a fixed effect and the tested eye as a random effect.

Results

As anticipated, dark adaptation curves measured with the 640 nm stimulus were monophasic in all subjects (Figure 2), which is consistent with detection by the cones. Patients with MacTel had elevated thresholds to 640 nm targets at all time points; however, this was not simply an upward translation of the adaptation curve, thus suggesting that an isolated *d3* mechanism loss cannot account for the changes in threshold. Curves obtained with the 480 nm stimulus were biphasic in normal subjects, and although subjects with MacTel had evidence of rod participation in threshold detection beyond 10 minutes (on average), the data beyond this timepoint were insufficient to estimate the full-rod exponential decay function accurately (Figure 3).

Eyes with MacTel had significantly delayed cone adaptation kinetics compared with normal subjects, reflected by a greater value for τ (1.61 ± 0.39 minutes [mean ± SE] in normals vs. 4.44 ± 0.81 minutes in MacTel; $P = 0.002$). Patients with MacTel had elevated thresholds to 480 nm and 640 nm stimuli. Absolute cone thresholds for 640 nm targets were −2.24 ± 0.07 log Td versus −1.81 ± 0.10 log Td ($P < 0.001$). A larger elevation in 480 nm stimulus absolute thresholds between normal and MacTel patients was observed (−4.03 ± 0.17 log Td vs. −2.25 ± 0.10 log Td; $P < 0.001$), thus suggesting greater impairment of rod than cone thresholds in MacTel. There was no correlation between the Gass–Blodi clinical classification and the key dark adaptation parameters (Figure 4). Similarly, there was no correlation between the photoreceptor layer status on OCT and key dark adaptation parameters (τ, cone absolute threshold and 480 nm absolute threshold $P > 0.05$). These results suggest that impaired adaptation is an early and consistent feature of the condition.

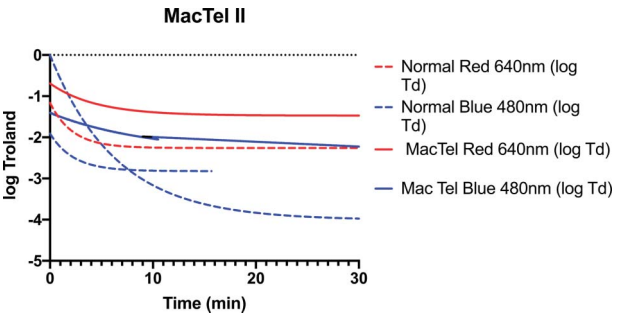

Fig. 2. Averaged dark adaptation curves for normal observers for Goldmann size V 640 nm (dashed red line) and 480 nm (two dashed blue lines; the upper represents cone-mediated detection and the lower, rod-mediated detection) and for subjects with MacTel (640 nm uninterrupted red line; 480 nm uninterrupted blue line). MacTel subjects demonstrate delayed cone adaptation kinetics as well as cone and rod sensitivity loss consistent with *d1/d2* mechanism loss. See text for details.

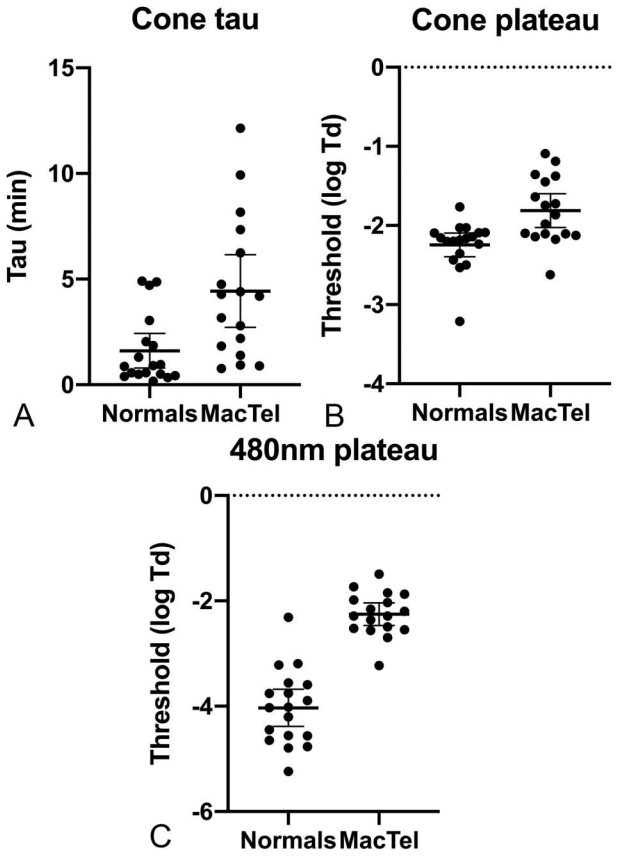

Fig. 3. A. Cone-mediated time constant of adaptation, tau, for normals versus MacTel patients reflecting a statistically significant delay in cone adaptation, tau (normal 1.52 ± 0.40 minutes [mean ± SEM] vs. 4.43 ± 0.81 minutes; $P = 0.002$).; **B.** Cone-mediated absolute thresholds for 640 nm stimuli demonstrating a statistically significant elevation in threshold in MacTel (−2.27 ± 0.07 log Td vs. −1.8 ± 0.1 log Td $P < 0.001$); **C.** 480 nm targets were statistically significantly elevated in patients with MacTel (−4.13 ± 0.14 log Td vs. −2.25 ± 0.10 log Td; $P < 0.001$).

Discussion

Consistent with previous studies of dark adaptation in patients with MacTel II,[11] we found that absolute rod threshold was affected more severely than cone absolute threshold for Goldmann size V targets presented within the MacTel zone at 2° nasal to fixation (i.e., temporal retina). In fact, it was not possible to determine the features of the early phases of rod recovery accurately in any of our subjects with MacTel (although the average dark adaptation curve for 480 nm stimuli demonstrated evidence of rod intrusion after 10 minutes). Because we could not accurately model rod responses in the earlier recovery phases in MacTel subjects, we cannot ascertain the mechanism of rod sensitivity loss based on our data (i.e., *d1/2* vs. *d3* sensitivity loss). Consistent with previous observations, we found no significant correlation between key dark adaptation parameters and Gass and Blodi classifications.[11,12] Furthermore, there was no significant correlation between photoreceptor layer disruption assessed by OCT imaging and dark adaptation parameters.

There was a significant elevation in cone absolute thresholds in eyes with MacTel. This decline in function was not consistent with an isolated *d3* mechanism loss, as the dark adaptation curve did not seem to be simply translated upward. Similarly, a simple filter effect, or so-called d*1/2* mechanism loss alone, cannot account for our observations. Although we anticipate no change in τ for small changes in bleaching, modeling of normative data (Figure 1) suggests that a significant (e.g., 90%) filter effect should result in an apparent shortening of the time constant of adaptation in cone photoreceptors (e.g., in Figure 1, a 1 log unit filter effect for a bleach of similar magnitude to that used in the current study results in an approximate halving of τ) together with a slight decrease in the span of responses (i.e., A, the span from the threshold at t = 0 minutes to plateau).

Although MacTel patients, on average, had a reduced A, this was not statistically significant (4.31 ± 1.09 log Td vs. 2.19 ± 0.41 log Td; $P = 0.07$). It will be noted that modeling data suggest that delay of cone adaptation kinetics would be manifest as an increase in A but would not change the value of absolute threshold (Figure 1); this may have obscured any d1/2 mechanism loss or filter effect in the early stages of adaptation. An attempt can be made to remove the differential effects of delayed adaptation by predicting the initial threshold in the presence of normal adaptation/regeneration kinetics in our subjects. If we assume that the proportion of photopigment bleached by a brief flash (i.e., too brief to be affected by perturbations in cone regeneration kinetics) is equivalent between MacTel and normal subjects, and in turn assume that the value for Q_e is constant (see above),[25] then we can calculate the value for the intensity to produce a steady-state 50% bleach using Equation 2. Using our data for MacTel patients in Equation 2 yields an I_0 of 3.8 log Td. This value can, in turn, be used to calculate the proportion of photopigment bleached according to Equation 3 mentioned above.[13] This leads us to predict an approximate average of 87% cone photopigment bleach in MacTel using our protocol. If we apply the data for bleaching in normal and MacTel patients to empirical data predicting threshold elevation by different bleaches,[16] and adjust the MacTel initial threshold data accordingly, then the difference in A between MacTel patients and normal patients is statistically significant (4.31 ± 1.15 log Td for normal vs. 1.72 ± 0.41 log Td for MacTel subjects; $P = 0.038$), supporting the hypothesis that there is a

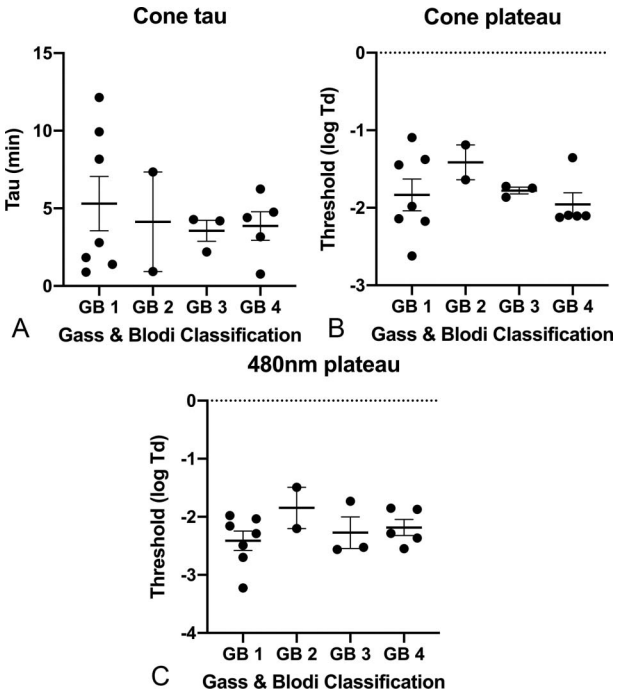

Fig. 4. Cone-mediated tau (**A**), cone absolute threshold (**B**), and rod absolute threshold (**C**) versus Gass and Blodi classification demonstrating no significant differences between groups (mixed-effects model all $P > 0.05$).

d1/d2 mechanism loss of cone sensitivity in MacTel, which is combined with delays in adaptation. This observation is consistent with histopathological examination and with adaptive optics imaging, which point to loss and disruption of the cone photoreceptor mosaic.[5,6,26] We cannot, however, completely exclude some contributions of *d3* mechanism loss, which would be predicted based on electrophysiological observations in MacTel.[27–30] It will be noted that increment threshold testing could also be used to determine the contribution of postreceptoral losses to threshold elevation.[23]

A filter mechanism of sensitivity loss acting alone would be predicted to result in either no alteration in kinetics (for small changes in bleaching) or a reduction in τ (for larger changes, based on empirical measurements; Figure 1). By contrast, we found a statistically significant delay, which in turn is consistent with delayed cone photopigment regeneration. What might underlie this finding? Because of the importance of the Müller cells in the maintenance of vision under photopic conditions/ in the rapid regeneration of the cone pigments, it is likely that this delay in cone adaptation reflects Müller cell pathology. However, although we know that the Müller cells are both important in cone photopigment regeneration and in the pathogenesis of MacTel, we cannot definitively exclude a contribution from RPE disruption or dysfunction.

Because there is a profound delay in cone adaptation kinetics in MacTel, it may potentially be used in the future as a biomarker for early functional changes. Furthermore, it may also serve as a suitable functional outcome measure in future studies of active interventions, especially because it is possible to assess cone adaptation and absolute threshold relatively easily (at the retinal locus evaluated in the current study) when compared with rod adaptation. However, it will be noted that our study is limited in its relatively small sample size. Furthermore, the control group tested was slightly younger than our MacTel participants. Finally, objective estimates of macular pigment optical density and distribution were unavailable; although variations in macular pigment would not affect results for the long-wavelength test stimulus, loss of macular pigment in MacTel patients may have minimized estimates of sensitivity loss for the 480 nm stimulus. Furthermore, there is some limited histopathological data to suggest that macular pigment optical density offers a surrogate measure of Müller cell loss[5] and could potentially be used to test the hypothesis that delayed cone adaptation reflects such loss.

In summary, there is a significant loss of absolute cone and rod threshold in MacTel, although rod impairment is on average greater than cone impairment. Furthermore, our data support the hypothesis that MacTel results in significantly delayed cone adaptation/cone photopigment regeneration, which is likely to reflect–at least in part—Müller cell dysfunction. Our data also point to a likely *d1/d2* mechanism of loss of cone sensitivity in MacTel if the effects of delayed adaptation are considered.

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