IMPAIRMENTS OF L-CONE/M-CONE AND S-CONE–MEDIATED COLOR DISCRIMINATION IN MACULAR TELANGIECTASIA TYPE II

MATTHEW P. SIMUNOVIC, MB, BCHIR, PHD,*† MARK C. GILLIES, MB, BS, PHD*†

Purpose: To characterize red–green and tritan color discrimination in eyes with macular telangiectasia Type II (MacTel).

Methods: Color discrimination was assessed by metameric matching methods using an Oculus MR Anomaloscope. Red–green color discrimination was assessed using the Rayleigh equation, and tritan color discrimination was assessed using the Moreland equation. Results were expressed as anomalquotient (AQ) and tritanomalquotient (TAQ) units, respectively.

Results: Seventeen eyes with MacTel were compared with 16 control eyes with normal vision. Twelve eyes with MacTel demonstrated abnormal color matches; except for two eyes with red-shifted Rayleigh matches, the primary abnormality evident was reduced color discrimination. On average, Rayleigh matching ranges were significantly widened in MacTel (0.518 ± 0.066 AQ units) compared with normal (0.14 ± 0.03 AQ units; $P < 0.0001$). Similarly, Moreland matching ranges were significantly wider (0.794 ± 0.109 TAQ units) than normal control subjects (0.204 ± 0.070 TAQ units; $P < 0.0001$). Losses in color discrimination did not correlate significantly with the best-corrected visual acuity, although Moreland matching ranges were significantly correlated to Rayleigh matching ranges.

Conclusion: MacTel results in a combined acquired red–green and tritan color vision deficiency. A minority of eyes demonstrated red-shifted Rayleigh matches, consistent with decreases in cone photopigment optical density.

RETINA 42:576–580, 2022

Reprint requests: Matthew P. Simunovic, MB, BChir, PhD, Save Sight Institute, University of Sydney, Sydney Eye Hospital South Block, 8 Macquarie Street, Sydney, NSW 2000, Australia; e-mail: mps23@cantab.net

Macular telangiectasia Type 2 (MacTel) is a bilateral but typically asymmetric disorder which affects up to one in 2,000 individuals over 40[1] first described as a distinct disease entity in 1977.[2] MacTel is associated with vascular abnormalities commencing 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] Although its name implies a primary vasculopathy, other changes precede vascular anomalies. These 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 epithelial migration and so-called right angle retinal vascular changes (resulting from vascularization of the outer retina) occur. MacTel may sometimes be associated with choroidal neovascularization or macular holes. Other lines of evidence suggest that the vasculature does not appear to be the primary site of pathology: Advanced imaging techniques and histopathological analysis implicate the early loss of both the macular pigment and the Müller cells of the retina.[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 photoreceptors (in addition to the Müller glia).[5] More recently, in vivo imaging of the foveal cones with adaptive optics scanning LASER ophthalmoscopy has elucidated loss of cones/disruption of the cone mosaic, even in early in the disease course.[6]

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.[7] Although there are data to suggest that MacTel generally results in greater deficits of rod compared with cone absolute threshold outside of the region of the visual field corresponding to the fovea, little is known about the differential effects of MacTel on cone-mediated vision within the central retina. Because of the paucity of data on color discrimination in MacTel, and the reported sensitivity of color vision in detecting retinal pathology,[8] we aimed to determine in detail the effects of MacTel on the M-cone versus L-cone (red–green) and S-cone versus M + L-cone (tritan) subsystems of color vision.

Methods

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

Participants

Subjects with MacTel (20 eyes from 11 patients; age range 47–85 years; mean age 62.8 years) with the logMAR best-corrected visual acuity ranging from −0.08 to 0.5 (mean 0.27) were classified according to the scheme proposed by Gass and Blodi[9] and were recruited after obtaining written informed consent. Three patients had diabetes mellitus, but no evidence of diabetic retinopathy or any other concurrent ocular conditions. Normal controls were recruited by local advertising (16 eyes from n = 8 patients; age range 38–85; mean age 50.8 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 Testing Protocol

All subjects underwent clinical examination, including assessment of the best-corrected visual acuity. In addition, dilated fundus examination (pupils dilated with 1% tropicamide and 2.5% phenylephrine, after evaluation of color discrimination) and spectral-domain optical coherence tomography were also performed.

Although discrimination tasks using Munsell paper-based/pigment-based tests, such as the FM D-15,[10] Roth 28Hue,[11] and FM 100Hue,[10] are often used to assess acquired color vision deficiency, they may fail to elucidate important phenotypes relevant to retinal pathology, such as pseudoprotanomaly and scotopization.[8] Similarly, computer-controlled visual display unit-based tests also suffer from some of the same disadvantages as pigment-based tests. Although they are highly specialized (and thus generally only available in clinical research settings) color matching tasks, by contrast, use monochromatic or near-monochromatic stimuli, which have the advantage of revealing the important phenotypes described previously.[8,12] Furthermore, their wavelengths can be carefully selected to minimize the effects of interindividual variations in prereceptoral light absorption. One of the issues with assessing tritan color discrimination in MacTel is that macular pigment is known to be depleted early in the disease process.[3] This may help to offset the loss of S-cone–mediated (tritan) color discrimination.[13] Although attempts may be made to account for such alterations by measuring macular pigment optical density, an alternative is to use tests designed to be less sensitive to variation in the pre-retinal ocular media. Accordingly, we used anomaloscopy (Oculus MR anomaloscope, Oculus GmbH, Wetzlar, Germany) to assess S-cone–mediated color vision using the Moreland Equation[13] and M-cone versus L-cone–mediated color vision using the Rayleigh equation.[14] In brief, these color mixing "equations" are presented as a 2° (Rayleigh equation) or 4° (Moreland equation) circular bipartite field presented in Maxwellian view.

The Rayleigh equation was first described by William Strutt (Lord Rayleigh) in 1881.[14] As used by the Oculus MR anomaloscope, the Rayleigh equation is presented as:

$$589 \text{ nm} = 549 \text{ nm} + 666 \text{ nm}$$

The subject must attempt to match in color and/or

brightness a monochromatic yellow light (589 nm) in the bottom half of a circular bipartite field to a mixture of monochromatic green (549 nm) with red (666 nm) light in the top half of the field.

The Moreland equation represents one of several attempts to employ an analogous metameric color match to explore tritan color discrimination.[12,13] Such matches are imperfect because the wavelengths used are affected by the preretinal media: One advantage of the Moreland equation is that the wavelengths used in the test field (436 and 490 nm in the so-called Moreland 2 equation)[15] were designed to minimize the known individual variations in the macular and lens pigments. The oculus anomaloscope presents the Moreland equation as:

$$480 \text{ nm} + 580 \text{ nm} = 436 \text{ nm} + 490 \text{ nm}$$

Here, the subject must attempt to obtain a match between a green–blue primary (480 nm) mixed with a fixed ratio of yellow–green (580 nm) presented in the bottom half of the bipartite field (which appears slightly desaturated green–blue to normal observers) to a mixture of violet (436 nm) and cyan (490 nm) in the top half.

All testing was performed with the instrument in the "absolute" setting to negate the effects of adaptation artifactually widening matching ranges. In this setting, the anomaloscope presents the matching field for 5-second intervals, in between which a neutral adapting field approximately standard illuminant C (correlated color temperature 6750 K) was presented for 3 seconds. Results for the Rayleigh equation were converted into anomalquotients:

$$AQ = \left(\frac{G_p}{R_p}\right) \times \left(\frac{R_n}{G_n}\right)$$

Where G_p is the green setting at the midmatching point of the patient, R_p is the red setting, and G_n and R_n are the green and red settings at the midmatching points of healthy patients.

Results at the Moreland equation were converted into tritanomalquotients:

$$TAQ = \left(\frac{V_p}{C_p}\right) \times \left(\frac{C_n}{V_n}\right)$$

Where C_p is the cyan setting at the midmatching point of the patient, V_p is the violet setting, and C_n and V_n are the cyan and violet settings at the midmatching points of healthy patients. Key variables were summa-

rized as means ± standard errors. Statistical comparisons were conducted in SPSS (IBM, Armonk, NY) using a linear mixed effects model, with diagnosis (MacTel vs. normal) set as a fixed effect and the tested eye as a random effect.

Results

Our subjects with MacTel were able to perform both Rayleigh and Moreland matches satisfactorily at the oculus anomaloscope, with the exception of one patient, who was unable to perform the test with his worse-seeing eye (best-corrected visual acuity 20/200). One further eye was excluded as it had previously undergone implantation of a ciliary neurotrophic factor implant. Only two eyes had mid-matching points outside the 95% limits for normal controls for the Rayleigh equation (Figure 1). Furthermore, their mid-matching points were shifted toward the left, which is consistent with decreased cone photopigment optical density.[8,16,17] No eyes with MacTel had Moreland mid-matching points outside the 95% limits for normal controls. On average, the midmatching points at the Rayleigh equation in MacTel did not differ significantly from those of normal controls 1.09 ± 0.04 versus 1.02 ± 0.08, respectively ($P = 0.421$). Similarly, the
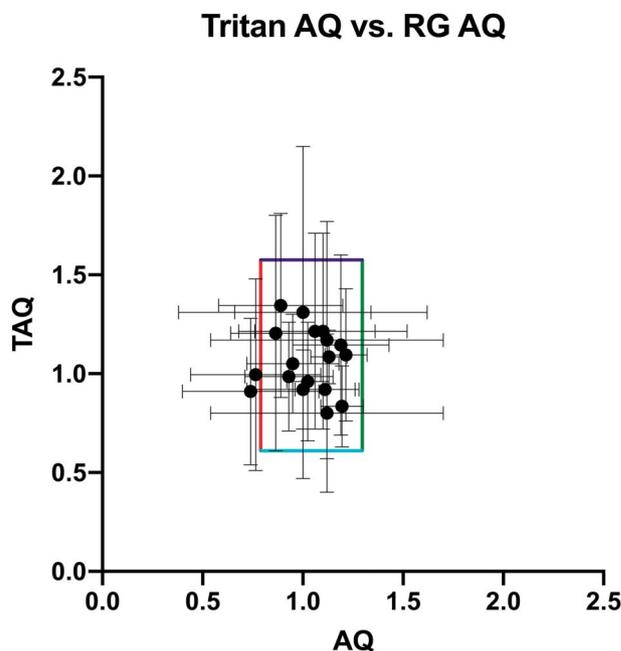

Tritan AQ vs. RG AQ

Fig. 1. Moreland versus Rayleigh matches expressed as tritanomalquotients and anomalquotients, respectively. Dots represent midmatch points, and bars indicate matching ranges. The colored box represents the 95% confidence intervals for normal matching ranges. A total of two eyes have red-shifted Rayleigh matches, consistent with decreased cone photopigment optical density. AQ, anomalquotient; TAQ, tritanomalquotient.

midmatching point for the tritanomalquotient did not differ significantly between eyes with MacTel (1.02 ± 0.03) and normal (1.06 ± 0.04; $P = 0.437$).

Only 5 of 20 eyes with MacTel demonstrated matching ranges within the 95% limits for normal at both the Rayleigh and Moreland matches; 3 eyes had isolated widening of the Rayleigh match, and 12 eyes had combined widening of the Rayleigh and Moreland matches (Figure 2). On average, Rayleigh matching ranges were significantly widened in MacTel (0.518 ± 0.066) compared with normal controls (0.14 ± 0.03; $P < 0.001$). Similarly, Moreland matching ranges were significantly widened (0.794 ± 0.109) compared with normal control subjects (0.204 ± 0.070; $P < 0.001$).

Rayleigh and Moreland matching ranges did not correlate significantly with the best-corrected visual acuity (Spearman R = 0.423; $P = 0.07$ and R = 0.372; $P = 0.13$, respectively); however, a statistically significant correlation was observed between Rayleigh and Moreland matching ranges (Spearman R = 0.72, $P < 0.001$). Similarly, there was no significant correlation between Gass and Blodi disease stage and either Rayleigh (Spearman R = 0.323; $P = 0.182$) or Moreland matching ranges (Spearman R = 0.455; $P = 0.39$; Figure 3).[9]

Discussion

Although patient-reported quality of life measures do not suggest that impairments of color discrimination are a major feature of MacTel,[3] most eyes we assessed had color vision abnormalities, suggesting that it may be a

Fig. 3. Moreland (A) and Rayleigh (B) matching ranges plotted against Gass and Blodi classifications. Bars represent means. AQ, anomalquotient; TAQ, tritanomalquotient.

common—but hitherto undocumented—feature of the condition. Impairments in both the M-cone versus L-cone and S-cone versus M + L-cone subsystems of color vision were evident in most eyes with MacTel. However, these alterations are in general subtle compared with the profound alterations reported in paracentral increment threshold testing probing cone and rod sensitivity.

Although alterations to cone morphology have been reported on adaptive optics imaging, pseudo-protanomaly does not appear to be a common feature of eyes with MacTel. For example, only two eyes demonstrated red-shifted midmatching points on the Rayleigh match. This phenomenon is believed to result from losses of cone photopigment optical density, which may be from reductions in the photo-pigment concentration or through alterations in the outer segments, including shortening and misalignment.[8] Interestingly, no eyes demonstrated isolated losses of tritan discrimination, as reflected by a widening of the Moreland matching range. Pinckers and Marre[18] have previously proposed that in conditions where there is early involvement of the central retina, red–green (M-cone vs. L-cone) color vision deficiency is generally observed. By contrast, retinal diseases with early involvement of the paracentral retina tend to result in preferential involvement of the S cones and, therefore, an acquired tritan (S-cone vs. M + L-cone) color vision deficiency. MacTel therefore represents an exception to the Pinckers and Marre hypothesis [18,19]: Most eyes with MacTel demonstrated widened Rayleigh and Moreland matches, which the exception of those eyes which show an isolated widened Rayleigh match. This may in part be explained by alterations in macular pigment concentration as a result of the disease process (i.e., any loss of S-cone–mediated sensitivity is offset by improved discrimination derived through lower absorption of light by macular pigment). As noted above, the Moreland match was developed to mini-mize the effects of individual variations in the
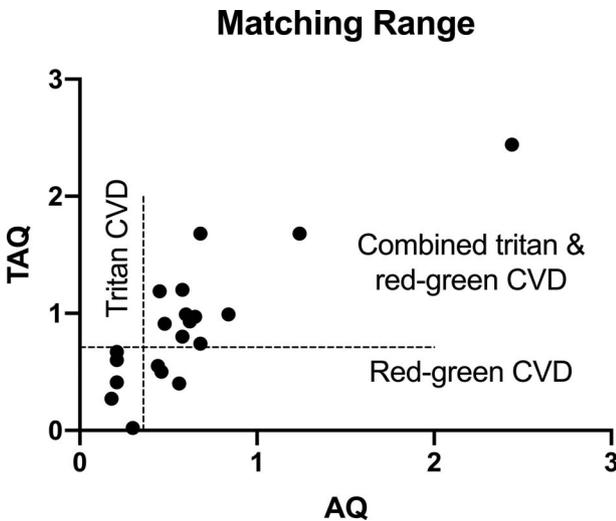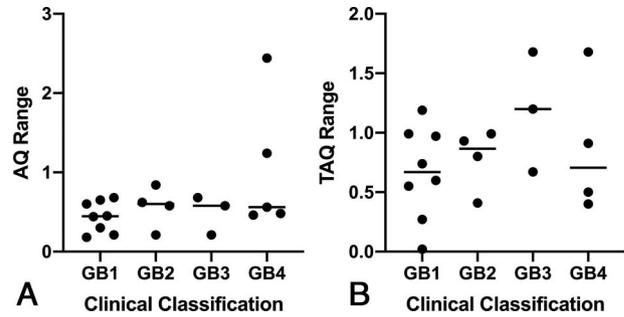
Matching Range

Fig. 2. Absolute Moreland matching ranges (in TAQ units) plotted against Rayleigh matches (in AQ units). 15 of 20 eyes with MacTel have matching ranges outside of the 95% confidence intervals for normal (dashed lines); of these, 12 have both widened Rayleigh and Moreland matches, whereas three have widened Rayleigh matches alone. AQ, anomalquotient; TAQ, tritanomalquotient.

prereceptoral ocular filters; however, it is not entirely impervious to such alterations.[13]

In summary, most eyes with MacTel have evidence of nonselective abnormalities of both the M-cone versus L-cone and S-cone versus M + L-cone subsystems of vision. However, these alterations are comparatively subtle compared with the profound alterations in paracentral cone–mediated and rod-mediated threshold sensitivity.[20,21] In contrast to other conditions affecting the paracentral retina,[18,19] loss of S-cone–mediated discrimination does not appear to be a prominent feature of MacTel. However, as noted above, losses in S-cone–mediated sensitivity may be offset by decreases in macular pigment optical density, which are a characteristic of this condition.

Key words: macular telangiectasia, Rayleigh match, Moreland match, acquired color vision deficiency.

References

1. Klein R, Blodi BA, Meuer SM, et al. The prevalence of macular telangiectasia type 2 in the Beaver Dam eye study. Am J Ophthalmol 2010;150:55.e2.
2. Gass JD. Stereoscopic Atlas of Macular Diseases. St. Louis, MI: Mosby Yearbook; 1977.
3. Charbel Issa P, Gillies MC, Chew EY, et al. Macular telangiectasia type 2. Prog Retin Eye Res 2013;34:49–77.
4. Gantner ML, Eade K, Wallace M, et al. Serine and lipid metabolism in macular disease and peripheral neuropathy. N Engl J Med 2019;381:1422–1433.
5. Powner MB, Gillies MC, Zhu M, et al. Loss of Müller's cells and photoreceptors in macular telangiectasia type 2. Ophthalmology 2013;120:2344–2352.
6. Song H, Rossi EA, Williams DR. Reduced foveal cone density in early idiopathic macular telangiectasia. BMJ Open Ophthalmol 2021;6:e000603.
7. Heeren TF, Clemons T, Scholl HP, et al. Progression of vision loss in macular telangiectasia type 2. Invest Ophthalmol Vis Sci 2015;56: 3905–3912.
8. Simunovic MP. Acquired color vision deficiency. Surv Ophthalmol 2016;61:132–155.
9. Gass JD, Blodi BA. Idiopathic juxtafoveolar retinal telangiectasis. Update of classification and follow-up study. Ophthalmology 1993;100:1536–1546.
10. Farnsworth D. The farnsworth-munsell 100-hue and dichotomous tests for color vision. J Opt Soc Am 1943;33:568–578.
11. Amos JF, Piantanida TP. The Roth 28-hue test. Am J Optom Physiol Opt 1977;54:171–177.
12. Dain SJ. Clinical colour vision tests. Clin Exp Optom 2004;87: 276–293.
13. Moreland JD. Moreland match revisited. Vis Neurosci 2004; 21:471–476.
14. Rayleigh. Experiments on colour. Nature 1881;25:64–66.
15. Moreland JD, Kerr J. Optimization of a Rayleigh-type equation for the detection of tritanomaly. Vis Res 1979;19:1369–1375.
16. Simunovic MP, Hess K, Avery N, Mammo Z. Threshold versus intensity functions in two-colour automated perimetry. Ophthalmic Physiol Opt 2021;41:157–164.
17. Simunovic MP, Xue K, Jolly JK, MacLaren RE. Structural and functional recovery following limited iatrogenic macular detachment for retinal gene therapy. JAMA Ophthalmol 2017;135:234–241.
18. Pinckers A, Marré M. Basic phenomena in acquired colour vision deficiency. Doc Ophthalmol 1983;55:251–271.
19. Marré M, Pinckers A. Basic phenomena of acquired color vision defects. Bull Soc Belge Ophtalmol 1985;215:17–25.
20. Tzaridis S, Hess K, Heeren TF, et al. Dark adaptation in macular telangiectasia type 2. Retina 2020;40:2018–2025.
21. Heeren TF, Tzaridis S, Bonelli R, et al. Dark-adapted two-color fundus-controlled perimetry in macular telangiectasia type 2. Invest Ophthalmol Vis Sci 2019;60:1760–1767.