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ORIGINAL ARTICLE

Mechanisms of cone sensitivity loss in retinitis pigmentosa

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Abstract

Purpose: To explore the mechanisms of cone sensitivity loss in retinitis pigmentosa by combining two-colour perimetry with threshold versus intensity (tvi) testing.

Methods: Seven subjects with autosomal recessive retinitis pigmentosa and 10 normal subjects were recruited and underwent perimetric testing of one eye using 480- and 640-nm Goldman size V targets presented under scotopic conditions (no background illumination) and against a white background ranging in luminance from –1.5 to 2 log cd m^{-2} in 0.5 log cd m^{-2} steps. Data were fitted with tvi functions of the form $\log T = \log T_0 + \log ((A + A_0)/A_0)^n$, where T is the threshold, T_0 is the absolute threshold, A is the background intensity, A_0 is the 'dark–light' constant and n is a gain constant.

Results: Reliable tvi functions could not be obtained within the region of the visual field corresponding to loss of the ellipsoid zone on optical coherence tomography. At fixation, changes in both T_0 and A_0 were observed, consistent with a d_1 mechanism loss, which resulted in an upwards and rightwards shift of the tvi function. Losses at [±3°, ±3°] demonstrated changes in T_0, consistent with a d_3 mechanism loss, resulting in an upwards translation of the tvi curve.

Conclusions: Although the absolute cone threshold was elevated at each location, shifts in the tvi function (so-called d_1 mechanism loss) at fixation minimise threshold elevation in the presence of white adapting backgrounds, such as those typically employed in standard two-colour perimetry. At more peripheral testing locations, changes in threshold occurred independent of background luminance (so-called d_3 mechanism loss). These findings suggest that backgrounds which selectively adapt rods while maintaining cones at, or near, absolute threshold may be preferable to conventional two-colour perimetry for assessing loss of cone sensitivity, especially at the point of fixation.

KEYWORDS
cone sensitivity, retinitis pigmentosa, rod–cone dystrophy, selective perimetry, threshold versus intensity, two-colour perimetry

INTRODUCTION

Inherited retinal disease (IRD) affects up to 1 in 3000 individuals and is now reported to be the commonest single cause of blindness registration in those of working age.[1] Although IRDs demonstrate significant genetic heterogeneity—with more than 300 genes and loci identified to date[2]—they can be classified phenotypically into around seven broad groups,[3] the commonest of which is rod–cone dystrophy (RCD; also known as retinitis pigmentosa, Human Phenotype Ontology identifier HP:0000510).[3] One of the hallmarks of this phenotypic category is early nyctalopia (loss of scotopic vision), reflecting the loss of rod photoreceptor function. However, with disease progression, this is followed by loss of photopic vision as a consequence of cone dysfunction and degeneration. The latter is argued to be the most important functional consequence of RCD,[4] and it may occur

by a variety of mechanisms that are incompletely understood. However, one critical player has been identified as an inactive thioredoxin and has been termed 'rod-derived cone viability factor' (RdCVF).[5] Transplantation of healthy rods into the sub-retinal space in murine models of IRD has been demonstrated to improve cone survival,[6] and RdCVF gene therapy has also been shown to enhance cone survival.[7] In addition to 'bystander' loss of cone photoreceptors in retinitis pigmentosa, there are waves of remodelling downstream of the photoreceptors, which themselves may impair function.[8] As cone-based vision is crucial for day-to-day visual function, it stands to reason that it may be important in monitoring disease progression and also in assessing emerging treatments for retinal degeneration.

The preferred means of topographically assessing rod versus cone function in IRD has been via so-called two-colour perimetry. This approach was initially developed in the 1980s for separating rod- and cone-mediated responses in patients with inherited retinal degenerations at a time when this could not be done effectively in a spatially resolved manner electrophysiologically.[9,10] Two-colour perimetry involves visual field testing with large short-wavelength (e.g., Goldmann size V, blue) ± long-wavelength (e.g., Goldmann size V, red) targets under scotopic conditions to isolate the rods.[9,10] Long-wavelength (e.g., Goldmann size V or III, red) targets are subsequently presented on a white background under photopic conditions (typically 10 cd m^{-2}) to suppress the rods and isolate the cones.[9,10] Analysis of spectral sensitivities suggests that each of these paradigms isolates the mechanism of interest by at least 2 log units (20 dB) in normal observers (assuming scotopic perimetry is conducted with only short-wavelength targets; under scotopic conditions, long-wavelength targets at >640 nm isolate the cones poorly).[11] However, testing with more than two wavelengths may be required to determine definitively the mechanism being probed in patients with retinal disease.[11]

One consequence of using white backgrounds to suppress rod sensitivity in two-colour perimetry is concurrent cone light adaptation. We recently employed threshold versus intensity (tvi) perimetric testing to demonstrate that this technique introduces asymmetries in adaptation whereby the rods are assessed at absolute threshold, while the cones are probed under conditions where Weber's law holds.[12] It has been argued that this asymmetry will favour detection of rod defects in patients with outer retinal pathology.[12] This is because such pathology is believed to cause so-called d_1 and d_2 (d, disease) mechanism loss,[13] which result in an upwards and rightwards shift of the tvi curve. Such losses in sensitivity may only become apparent when photoreceptor sensitivity is probed at, or near, absolute threshold.[12] In two-colour perimetry, where rod sensitivity is probed at absolute threshold and where cone sensitivity is probed under conditions where Weber's law holds, losses of cone sensitivity may evade detection.[12] In contrast, losses in sensitivity occurring the presumed site of 'gain' control results in upwards shifting of the tvi curve (so-called d_3 mechanism loss). Such losses in sensitivity will be evident regardless of the state of adaptation of the mechanism probed because threshold is elevated uniformly, regardless of adaptation (for a full discussion, see Simunovic et al.).[12]

Key points

- Retinitis pigmentosa/rod–cone dystrophy results in losses to cone sensitivity, which have a significant impact on functional vision.
- Losses in cone sensitivity in retinitis pigmentosa/rod–cone dystrophy may only become evident under conditions where cones are dark-adapted.
- Currently employed clinical tests of cone sensitivity may fail to detect loss of sensitivity in retinitis pigmentosa/rod–cone dystrophy.

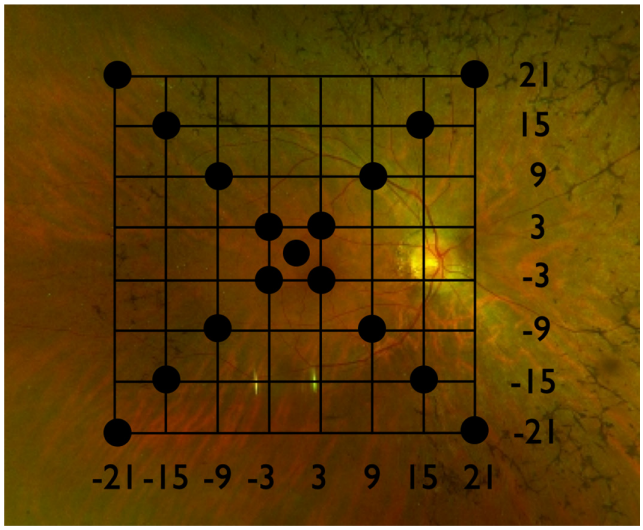

FIGURE 1 Fundus projection of the points tested with Goldman size V red (640 nm) and blue (480 nm) targets. Black spots represent the locations assessed; x- and y-axis markings represent degrees.

The possible sites of loss of cone-mediated sensitivity have previously been explored in a cohort of patients with RCD of unknown genotype by assessing tvi functions.[14] Such testing has been proposed to reveal differential effects of adaptation on threshold. As alluded to above, loss of sensitivity at the receptoral level (so-called d_1 and d_2 mechanism loss) is hypothesised to result in equal upwards and rightwards translation of the tvi function.[12-14] Post-receptoral losses of sensitivity—so-called d_3 mechanism loss, occurring at the level of the 'gain mechanism'—is hypothesised to result in an isolated upwards translation. Psychophysical and electrophysiological evidence of so-called d_3 mechanism loss was seen in a group of RCD patients using a long-wavelength flickering stimulus.[14] The favoured hypothesis of this observation was that RCD resulted in a loss of cone photoreceptors with preservation of some cones with normal outer-retinal adaptation properties. An alternate hypothesis is that some of the defects

may reflect a loss of sensitivity occurring at a putative 'second site' which, although post-receptoral, may be in the outer retina. Adaptive optics imaging of subjects with retinitis pigmentosa has demonstrated that while foveal cone density and structure in some patients may be normal, cone density may be reduced by up to two-thirds in patches of the foveal cone mosaic in patients who nevertheless possess normal visual acuity,[15] in keeping with previous histopathological observations of patients with IRD.[16] Furthermore, there may be profound structural abnormalities in the surviving cones in some subjects.[17] Regardless of the anatomical sites of loss, the effects of retinal disease on the tvi function are important because the disease processes leading to a so-called 'filter effect' may fail to elucidate loss of photoreceptor function if the visual system is tested under conditions where Weber's law holds.[12] The aim was to explore the mechanisms of cone sensitivity loss in RCD by assessing tvi functions using a two-colour paradigm[12] in a group of phenotyped and genotyped patients.

METHODS

Subjects

This study was approved by the local research ethics committee (South Eastern Sydney Local Health District Ethics approval number 2019/ETH04754) and adhered to the tenets of the declaration of Helsinki.

Rod–cone dystrophy

We recruited seven subjects diagnosed with retinitis pigmentosa/rod–cone dystrophy who had undergone genetic testing (see Table 1). Of these, six were able to complete psychophysical testing. The average age of the tested subjects was 40.1 years (range: 23–59 years). Testing was undertaken monocularly on the better-seeing eye; mean best-corrected visual acuity (BCVA) was 0.04 logMAR; range −0.30 to 0.40 logMAR. Clinical examination consisted of anterior and posterior segment assessment, measurement of intraocular pressure using rebound tonometry and colour vision assessment with the Oculus MC anomaloscope (oculus.de). All subjects had typical findings of RCD/RP, including symptoms of nyctalopia, loss of peripheral field and evidence of peripheral retinal pigment epithelial (RPE) alterations/migration. None had evidence of posterior subcapsular cataract or other media opacity. Genotype and phenotypical characteristics of subjects are summarised in Table 1.

Normal control subjects

A total of ten normal control subjects aged 16–45 years were also tested. All subjects had a corrected visual acuity of logMAR 0.00 (6/6) or better, normal ophthalmic examinations and had normal colour vision as screened by the Ishihara Test for Colour Blindness and Oculus MC anomaloscope. All were in good systemic health and were not taking any medications with known ocular or neurological side effects.

Psychophysical testing and model predictions

Testing was undertaken following 40 min of dark adaptation from ambient indoor illumination levels in a light-sealed room. Patients and normal control subjects then

TABLE 1 Summary of clinical characteristics of rod–cone dystrophy (RCD) subjects.

Subject	Eye	Age (years)	Gene	BCVA (logMAR)	Rayleigh match	Moreland match
I	L	39	MAK (HoZ) (MAK-Alu insertion, exon 9)[a]	−0.30	N	N
II	R	32	ZNF408 (CHZ) (c.1621 > T;p.Arg541Cys[b]/c.1622;p. Arg541His)	0.00	N	N
III	R	42	USH2A (CHZ) (c.1876C > T;p. Arg626[b]/c.5298 + 1_5299-1_5572 + 1_5573-1del)	0.10	N	N
IV	L	46	USH2A (CHZ) (c.4645C > T;Arg1549X/ c.11864G > A; Tyr3955X)	0.40	W	W
V	R	49	Usher 2 phenotype	0.00	N	SW
VI	R	59	USH2A (HoZ) (c.10073G > A;p.Cys3358Tyr)	0.00	N	N
VII	L	54	MYO7A (HeZ) (c.1969C > T; p.Arg657Trp/c.569; p.Leu190Trp)	0.10	N	N

Abbreviations: BCVA, best corrected visual acuity; CHZ, compound heterozygote for disease-causing mutations; HeZ, heterozygous for 2 disease-causing mutations; HoZ, homozygous for disease-causing mutations; L, left eye; LogMAR, log10 of the Minimum Angle of Resolution; MAK, Male germ cell Associated Kinase; MYO7A, myosin VIIA gene; N, normal; R, right eye; SW, slightly widened; USH2A, Usherin/Usher 2A; ZNF408, ZiNc Finger protein 408.

[a]See Bujakowska et al.[19]

[b]Reported association with RP/RCD in the homozygous state.[20]

underwent sequential tvi perimetry using a MetroVision MonCVOne CR Perimeter (metrovision.fr) to assess sensitivity at the point of fixation [0°, 0°] and at 16 points outside of fixation [±3°, ±3°], [±9°, −9°], [−15°, −15°] and [−21°, 21°] (Figure 1). Testing commenced under scotopic conditions and then with the addition of a neutral/white adapting background from −1.5 log cd m^{-2} increasing in 0.5 log cd m^{-2} steps up to 2.5 log cd m^{-2} (CIE 1931 chromaticity diagram co-ordinates of the background $x = 0.329$, $y = 0.338$; constant down to −2.9 log cd m^{-2}). Threshold was determined for blue (480 nm) and red (640 nm) Goldmann size V (1.7° diameter circular) targets, which were produced by placing narrowband interference filters in the optical pathway of the projected stimuli (10 nm full width at half maximum). Threshold was determined using a 4-2-2 dB interleaved staircase algorithm similar to that previously described.[11,12] Two test runs were performed before commencing the experiment and breaks were permitted between tests, according to subject preference. After completion of tests, background and threshold values were converted into trolands, based upon averaged automated pupil size measurements using the MonCVOne perimeter and known luminance values. Data were then fitted using a least-squares method in GraphPad Prism (graphpad.com) with tvi curves of the form:

$$\log T = \log T_0 + \log\left(\left(A + A_0\right)/A_0\right)^n$$

where T is the threshold, T_0 is the absolute threshold, A is the background intensity, A_0 is the 'dark–light' constant and n is a gain constant ($n = 0.5$ reflects DeVries–Rose adaptation, $n = 1$ reflects Weber adaptation and $n > 1$ reflects saturation). Because our previous experiments suggested that n ranges from 0.81 (peripherally) to 0.94 (at fixation) for the M + L cone luminance mechanism,[12] combined with the fact that assuming Weber adaptation does not significantly alter the goodness of fit for the tvi curves, n was assumed to be 1. This is in keeping with previous studies of cone function assessed in clinical subjects using tvi testing.[14,18] The best-fitting model in terms of T_0 and A_0 was based upon the adjusted R^2 at each fitted test eccentricity as described previously.[12] T_0 for the 640-nm stimulus—which is predicted to be impervious to individual variations in the optical density of the pre-retinal filters—was presumed to better reflect cone sensitivity, and was used in comparisons between normal subjects and those with RCD/RP. A_0, which is presumed to be constant for each mechanism regardless of the wavelength employed to test threshold, was averaged for the 640- and 480-nm stimuli in the analysis. As discussed above, d_1 and d_2 losses of retinal sensitivity lead to an equal upwards and rightwards shift of the tvi curve, reflected by an equal increase in T_0 and A_0. By contrast, a d_3 mechanism loss leads an upwards shift in the tvi curve, reflected by an increase in T_0, but not A_0.

Testing was conducted monocularly (in better seeing eyes with RCD/RP) with the MonCVOne Perimeter in a specially designed dark room. Calibration checks were performed with an Ocean Optics USB4000 spectroradiometer (oceaninsight.com).

Imaging

All patients underwent ultra-widefield '3 colour' and fundus autofluorescence (FAF) imaging with an Optos fundus camera (optos.com) and optical coherence tomography (OCT) with a Zeiss Cirrus HD-OCT 5000 (zeiss.com; macular cube 512 × 128 scan and 21-line raster). OCT scans were scrutinised qualitatively for the presence or absence of the ellipsoid zone, and, if present, for any disruptions. In assessing OCTs and FAF images, the semi-automated scaling system of the MonCVOne perimeter was employed to predict testing locations. Briefly, this system scales imported images based upon the locations of the centre of the fovea and the optic nerve head, as determined by the examiner.

RESULTS

We were able to obtain thresholds to generate tvi curves for stimuli within the central 9 degrees of the visual field (i.e., at fixation and at the points [±3°, ±3°], see Figure 2) in six of the seven RCD subjects, but not beyond (due to insufficient data points because subjects were unable to see the brightest stimuli). In each case, the ellipsoid zone was found to be intact within the retinal area corresponding to the points tested, but not outside. One subject (IV) could not respond reliably to any stimuli at the minimum background luminance for testing, and their data were not included. For this subject, there was clear evidence of ellipsoid zone disruption within the areas of the retina corresponding to the visual field tested. Fitted curves, together with the averaged curves for 10 normal control subjects aged 16–46 years are shown in Figure 2.

Averaged data at the point of fixation were best fitted with a single tvi function in RCD subjects. The difference in thresholds between the 480-nm stimulus and 640-nm stimulus were consistent with detection by the M + L-cone mechanism: There was no evidence of a rod–cone transition or transition to an M versus L-cone mechanism in our subjects. Therefore, for comparison, we present data for the same mechanism in our normal subjects.[12] The best-fitting curves demonstrated an elevation in absolute M + L-cone thresholds by >0.6 log Trolands (Td) compared with normal subjects at the point of fixation, even though RCD patients had well-preserved visual acuity (average 0.04 logMAR, range −0.30 to 0.40). On average, the best-fitted tvi functions at fixation were consistent with an upwards and rightwards translation of the tvi curve (i.e., predominant filter effect, where the best-fitting tvi curve for RCD subjects nearly coincides with the tvi curve for normals at higher background

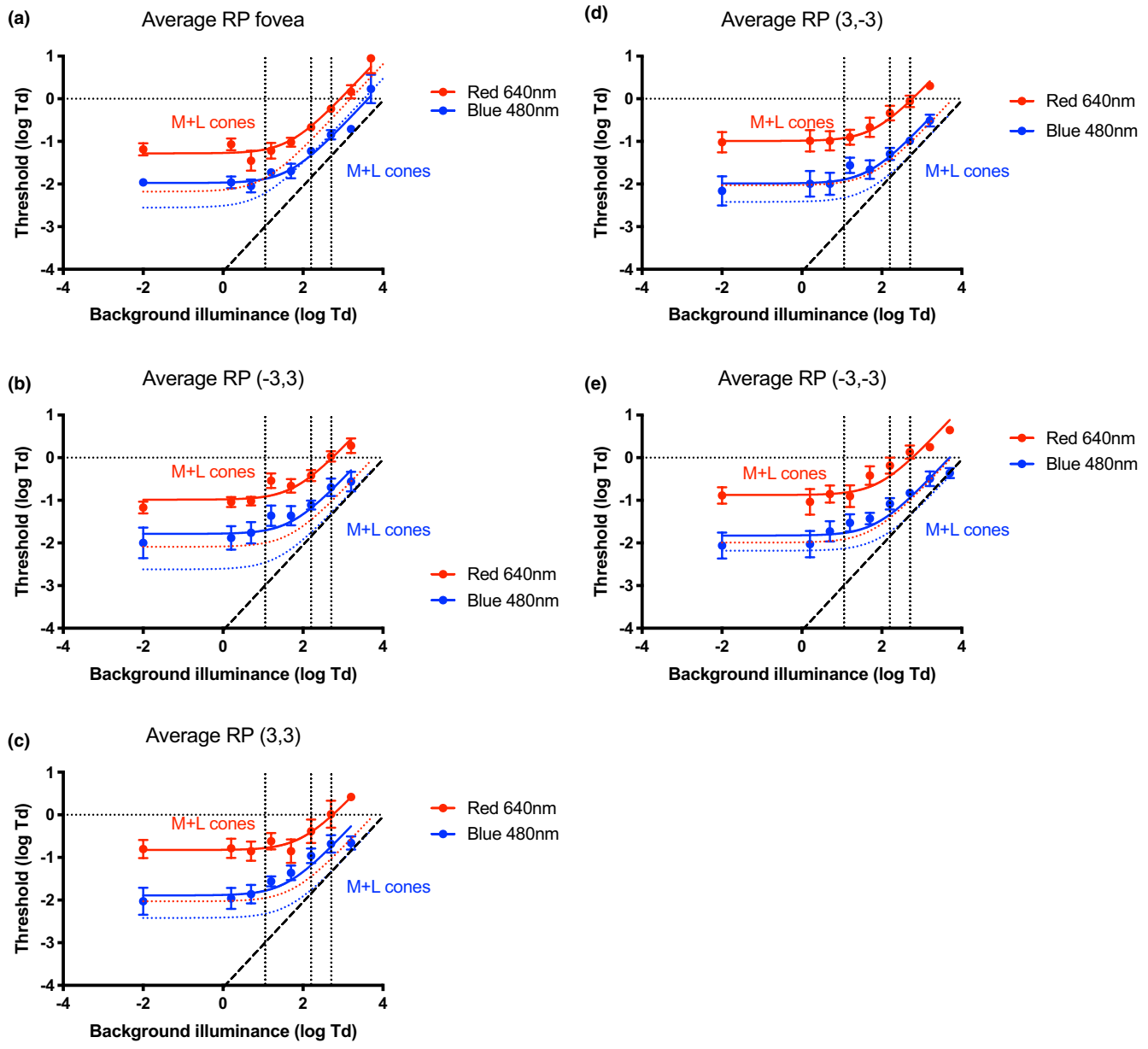

FIGURE 2 Threshold versus intensity functions for subjects with rod-cone dystrophy (RCD) / retinitis pigmentosa (RP) for 480-nm (mean ± SEM; blue circles) and 640-nm (mean ± SEM; red circles) Goldmann size V stimuli at the points of fixation (a) and for the Cartesian co-ordinates [±3°, ±3°] (b–e). The x-axis plots background luminance in log cd m^{-2} and the y-axis plots retinal illuminance in log troland. Averaged data for 10 normal subjects are plotted as interrupted lines (red—640 nm; blue—480 nm). Vertical dashed lines from left to right represent background light levels used in mesopic microperimetry, two-colour perimetry (natural pupil) and two-colour perimetry (dilated pupil).

intensities). When the difference in the threshold for the 640-nm stimulus—which was used as it is impervious to individual differences in the pre-retinal absorption by the lens and macular pigments—was plotted against the averaged A_0, the line of best fit was consistent with a predominant $d_{1/2}$ mechanism of sensitivity loss (line of best fit $A_0 = 0.8 \times T_0$; deviation from zero $F_{1,5} = 18.5$, $p = 0.008$), though it should be noted one subject's results were consistent with a d_3 mechanism loss (Figure 2a). Because of the small sample size in this study, it was impossible to determine if this loss correlated with genotype or disease severity.

For the more peripheral points that could be reliably fitted with tvi functions [±3°, ±3°], the averaged tvi curves (Figure 2b–e) did not demonstrate the cone–rod transition seen in normal subjects.[12] The difference in thresholds for the 480-nm and 640-nm targets were consistent with detection by an M + L-cone mechanism. Compared to normal data, the best-fitting tvi curves were translated vertically, consistent with a d_3 mechanism loss. This was confirmed by plotting A_0 versus T_0: linear regression did not find any statistically significant differences between the slope of the fitted line and $A_0 = 0$ (Figure 3). For all patients, the areas of retina which could detect

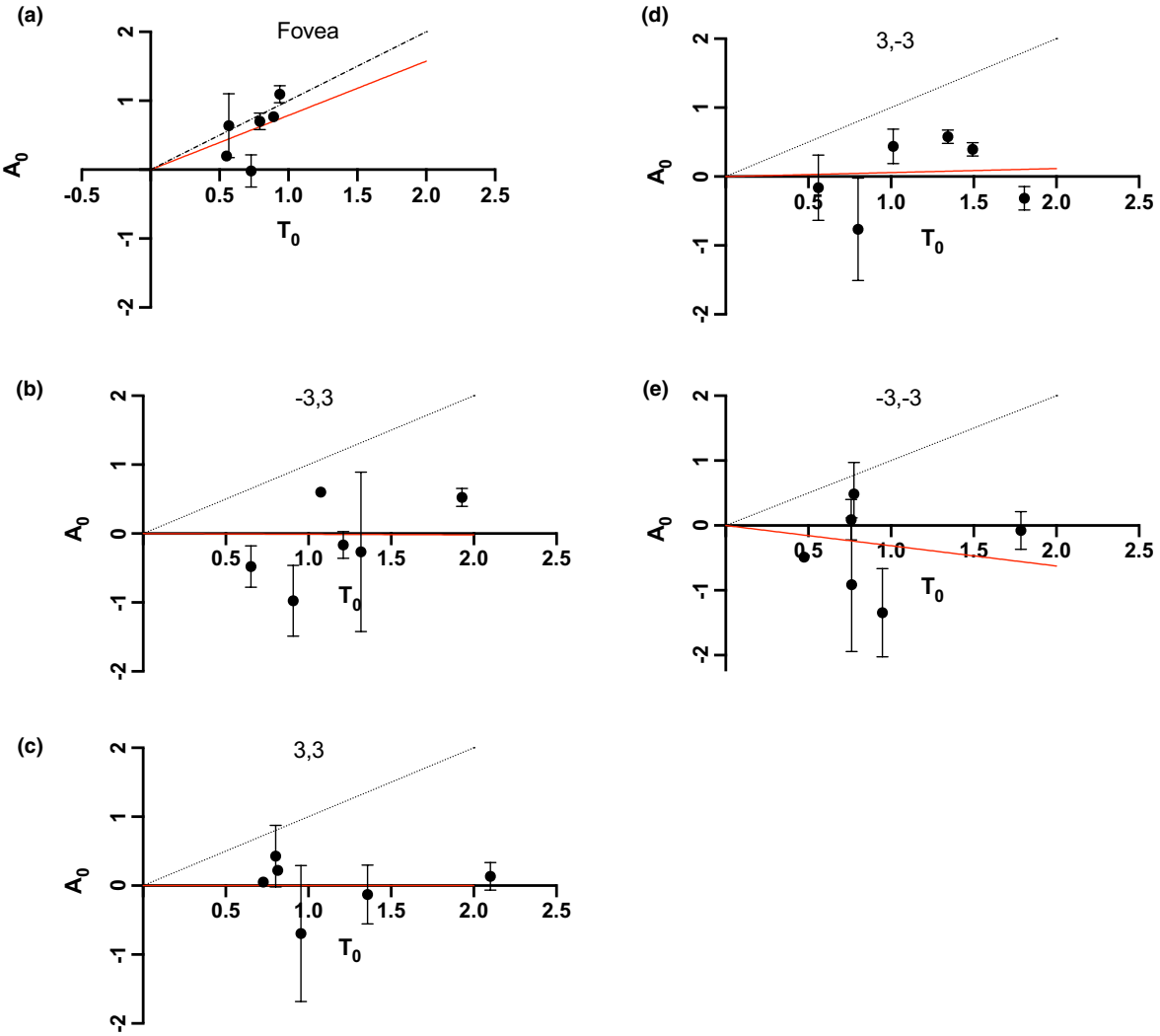

FIGURE 3 Change in absolute threshold (T_0-log troland) plotted against the 'dark-light' constant (A_0-log troland) for retinitis pigmentosa (RP) subjects at the point of fixation (a) and for the Cartesian co-ordinates [±3°, ±3°] (b–e). Points lying on the horizontal correspond to a pure d_3 mechanism loss in sensitivity. A line passing through (0,0) with a unitary slope (dotted black line) correspond to a d_1/d_2 (filter effect) mechanism. Red lines are the best-fitted straight line for subject data. Note that the latter only significantly differs from a zero slope at the point of fixation (line of best fit $A_0 = 0.8 \times T_0$; deviation from zero $F_{1,5} = 18.5$, $p = 0.008$).

the perimetric stimulus had preserved ellipsoids zones and outer nuclear layers on OCT scanning and preserved autofluorescence within the regions of preserved retinal sensitivity.

DISCUSSION

The general approach of using tvi functions to study in detail the possible level of pathology leading to losses in sensitivity was first developed by Hood and Greenstein and applied to the study of the rod photoreceptors,[13] and later applied to cones (M + L-cone mechanism).[14] Here, we combine this technique with two-colour perimetry to explore the mechanism of loss in sensitivity in patients with RCD/RP with known genotypes. We found abnormalities in the cone absolute threshold in all subjects at all locations tested, including those with visual acuities of logMAR 0.00 (6/6) or better. We also found that thresholds at all eccentricities were consistent with detection by a single additive M + L-cone mechanism. In contrast to the findings in normal subjects, we did not find evidence of intrusion by an M versus L-cone mechanism in RCD/RP at the point of fixation. One possibility is that this mechanism may be preferentially affected by pathology, though other possibilities cannot definitively be excluded. For example, where a d_1 mechanism of loss was present, an upwards and rightwards shift would be anticipated to shift the 'break' which occurs during the transition between detection mechanisms on the tvi plot. The nature of detection mechanisms in RCD/RP patients could be explored further using other approaches, such as determining the spectral sensitivity of detecting mechanisms,[11] employing higher background luminance for testing or noting participants' subjective experience of the test flash (i.e., achromatic vs. colour threshold).

Hood and Greenstein used the 500- and 660-nm circular 1° stimuli presented 7° nasal to the point of fixation (i.e., temporal retina) to explore rod tvi functions in subjects with IRD.[13] They found that participants with congenital stationary night blindness demonstrated a d_1 mechanism loss in rod-mediated sensitivity, but that data obtained from RCD/RP patients were not well described by a d_1 model.[13] Although the introduction of quantal noise into their modelling data resulted in their predicted tvi function in so-called d_2 mechanism loss to alter gain such that it fell between a d_1 and d_3 mechanism, this still did not describe the observed data of RCD/RP patients well. These observations led them to suggest a possible role for post-receptoral loss in sensitivity in RCD/RP.[13] Similarly, Seiple and colleagues measured tvi functions using a flickering 660-nm LED stimulus array subtending 9° in a Ganzfeld bowl to explore the mechanism of cone-mediated sensitivity loss in RCD/RP.[14] Their data suggested that the majority of patients demonstrated increased T_0 without a corresponding shift in A_0 (except for just one out of 11 subjects). They noted that loss of peripheral cones could not account for their observations because decreasing the stimulus size from 9° to 2° in normal subjects resulted in equal shifts in T_0 and A_0. They interpreted their findings in RCD/RP to indicate that there was a diffuse loss of cone photoreceptors within the field tested, and that the remaining photoreceptors had unaltered adaptation properties. The results in our subjects for the peripheral points tested were consistent with the findings of Seiple and colleagues.[14] If we assume that Seiple et al.'s[14] findings can be applied to a smaller test stimulus, then their hypothesis may account for our observations at the point of fixation, where five of our subjects demonstrated a $d_{1/2}$ mechanism loss. Specifically, their data can account for our observations if we accept that: (A) our results for peripheral stimuli represent a sparse loss of cone photoreceptors within the retinal loci corresponding to the stimulus and (B) results from central testing at fixation for a Goldmann size V (1.7° degree) target reflect the loss of cones from the edge of this testing field. The supposition of relative sparing of central cones is consistent with reports of preservation of retinal structure and cone function within the central visual field in large groups of RCD/RP patients tested with two-colour perimetric techniques at fixed predetermined photopic and scotopic levels by Jacobson and colleagues.[21]

Our experiments employed stimuli that were typically used to probe cone- and/or rod-sensitivity perimetrically.[9-12] As discussed previously, all patients demonstrated an elevated cone absolute threshold at all points tested. However, standard testing approaches, for example, so-called two-colour perimetry performed under scotopic and photopic conditions, typically do not isolate cone responses adequately to assess the absolute cone threshold.[11,12] In particular, the present findings demonstrate that for this group of RCD/RP subjects, losses in sensitivity outside of fixation would be anticipated to result in changes that would be detected using clinical two-colour perimetric protocols, as our participants demonstrated a so-called d_3 mechanism loss, resulting in an upwards translation of the tvi curve, which should be detectable regardless of the background testing level.[12] However, changes at the point of fixation were more consistent—in most subjects—with a filter effect/$d_{1/2}$ mechanism of loss. Thus, such changes may escape detection/or be minimised under standard clinical testing conditions (i.e., 'two-colour perimetry') designed to isolate cone from rod responses.[12] In the context of perimetric testing, this would potentially represent only a single test location, although it will be noted that any metric which weights the fovea might also be partially affected. This point should be taken into account when assessing threshold sensitivity as a measure of progression, or as a treatment effect, in emerging treatment paradigms. Accordingly, we propose that new approaches should be considered that differentially adapt the rods while leaving the cones in their dark-adapted state (e.g., through the use of a short-wavelength, rather than a white adapting background).[22]

AUTHOR CONTRIBUTIONS

Matthew P. Simunovic: Conceptualization (equal); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); supervision (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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