

# Reduced foveal cone density in early idiopathic macular telangiectasia

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## ABSTRACT

**Objective** Idiopathic macular telangiectasia (MacTel) is considered primarily a vascular disease affecting juxtafoveal retinal capillaries. However, recent evidence suggests that neuronal changes may occur early in disease development. We used high-resolution adaptive optics retinal imaging to elucidate the foveal cone photoreceptor changes at a cellular level in patients with MacTel.

**Methods and analysis** We used adaptive optics scanning light ophthalmoscopy (AOSLO) to evaluate the foveal cone photoreceptors in the less-affected eye of patients with asymmetric MacTel. AOSLO images of cone photoreceptors were obtained in a 4°×4° area centred on the foveola. Individual cone positions were identified within a 2°×2° area centred on the fovea, using semiautomatic cone marking software with manual correction, permitting calculation of a map of cone density.

**Results** In all participants, one eye was affected with MacTel, the fellow eye was clinically normal or near normal, with visual acuity of 20/25 or better and subtle angiographic leakage. The foveal cone mosaics were continuous with tight packing and cones exhibited normal reflectivity. However, cone density was significantly lower for all participants (mean=80 733 cones/mm<sup>2</sup>) within 0.5° than the cone density previously reported for normal eyes.

**Conclusions** Foveal cone density is lower than normal in the clinically less-affected eyes of patients with asymmetric MacTel. This suggests that cone photoreceptor loss may precede classic obvious vascular changes in idiopathic MacTel.

## INTRODUCTION

Idiopathic macular telangiectasia (MacTel) is considered a vascular anomaly affecting retinal capillaries in the juxtafoveal region of one or both eyes. It is characterised by slow but progressive loss of visual acuity, with morphological and functional changes being most pronounced on the temporal side of the foveola.<sup>1</sup> Although it has been considered a vascular disease, recent high-resolution imaging evidence suggests that neuronal changes at the photoreceptor layer may occur early in disease development.<sup>2 3</sup>

Currently no data are available on cone photoreceptor density at the foveal centre in patients with MacTel, the most important area for spatial vision. In the present study, we used adaptive optics scanning light ophthalmoscopy (AOSLO) to image the cone

## Key messages

### What is already known about this subject?

▶ Idiopathic macular telangiectasia (MacTel) is considered primarily a vascular disease affecting juxtafoveal retinal capillaries.

### What are the new findings?

▶ Using adaptive optics scanning light ophthalmoscopy (AOSLO) we found cone density was significantly lower in the clinically normal or near-normal eyes of the MacTel patients (mean = 80,733 cones/mm<sup>2</sup>) within 0.5 degrees than the cone density previously reported for normal eyes.

### How might these results change the focus of research or clinical practice?

▶ Cone photoreceptor loss may precede classic obvious vascular changes in idiopathic MacTel.

photoreceptors in and around the foveal centre in three patients with asymmetric MacTel type 2.

## METHODS

### Study participants and clinical examinations

Three participants (men, 61-year-old twins and age 35) with a diagnosis of type 2 MacTel (asymmetrical) were recruited for this study. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the University of Rochester research subjects review board. Informed written consent was obtained after a full explanation of the procedures and consequences of this study both verbally and in writing. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research. All subjects received a complete eye examination including fluorescein angiography. To accurately calculate the size of retinal features, axial length was measured with an IOL master (Carl Zeiss Meditec, Dublin, California, USA).

### AOSLO imaging, cone density measurements and statistical analysis

Cone photoreceptor images were acquired using an AOSLO system and methods described in detail elsewhere.<sup>4</sup> For all subjects

**Table 1** Clinical information of the three patients with MacTel

Patient	Age	Gender	Family history	MacTel eye	Less-affected eye	
1	61	Male	Twin brother (patient 2) affected	OD	OS	
2	61	Male	Twin brother (patient 1) affected	OD	OS	
3	37	Male	None	OD	OS	
Visual acuity		Ophthalmoscopic features		Fluorescein angiographic features		
	OD	OS	OD	OS	OD	OS
1	20/150	20/20	Pigment deposit, temporal greying	None	Temporal leakage	Normal
2	20/400	20/25	Greying, atrophy, cystic changes	Trace temporal greying	Early hyperfluorescence, late leakage throughout	Subtle temporal leakage
3	20/50	20/25	Retinal greying, right angle vessels, cystic changes	Subtle pigmentary stippling near fovea	Temporal leakage	Normal

MacTel, macular telangiectasia.

a  $\sim 3.5^\circ \times 3.5^\circ$  montage centred on the foveola was generated.

Every cone photoreceptor within a  $2^\circ \times 2^\circ$  area centred on the foveola was determined semiautomatically with a custom MATLAB program.<sup>5</sup> Manual editing of cone positions was performed to correct for errors in the automated algorithm. The size of retinal features was calculated

using the axial length of each participant scaled to the Gullstrand model eye.<sup>6</sup> The point of peak cone density was determined from the cone density map and considered the foveal centre. Using this position as a reference point, we then calculated cone density within  $36 \times 36 \mu\text{m}$  windows along each meridian from 0 to  $2^\circ$  at  $50 \mu\text{m}$  intervals. Two-way analysis of variance (ANOVA) was used to compare the AOSLO data to the AOSLO foveal cone data of Wang *et al*<sup>7</sup> and the interaction between retinal eccentricities.  $P < 0.05$  was regarded as a statistically significant difference.

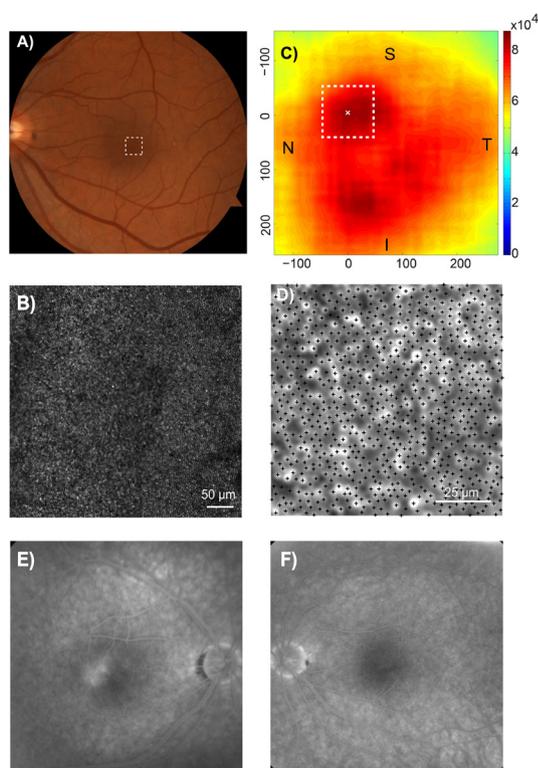
## RESULTS

### Clinical features

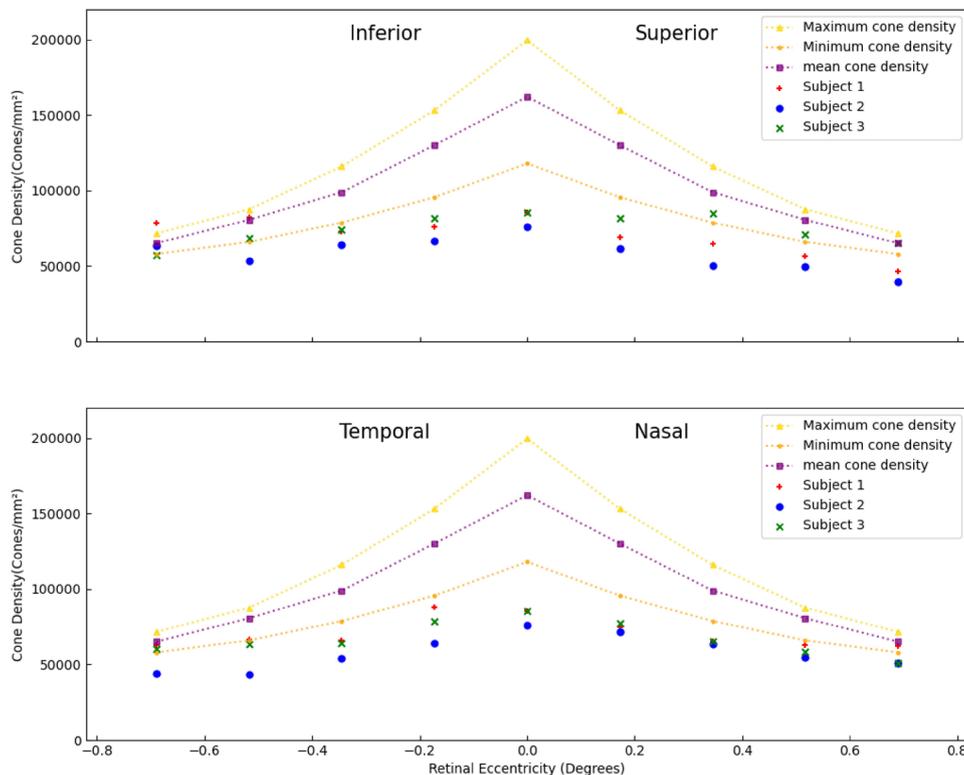
Table 1 lists the clinical information for these patients.

### Cone density is reduced at the fovea compared with normal eyes

The complete foveal cone mosaic was imaged in all three patients. Figure 1 shows the images from subject 1, clinical fundus image (panel A), foveal montages (panel B), density maps (panel C) and individual cone photoreceptors within a  $100 \times 100 \mu\text{m}$  window centred on the point of peak density (panel D), fundus fluorescein angiography (FFA) image of the affected eye (OD, panel E) and FFA image from the less-affected eye (OS, panel F). The cone images of subject 2 and subject 3 are shown in online supplemental eFigure 1. The peak cone density was  $84.7 \times 10^3$ ,  $71.8 \times 10^3$  and  $85.7 \times 10^3$  cones/ $\text{mm}^2$  for participants 1, 2 and 3, respectively. For comparison to expectations in a normal population, we compared these patients to the AOSLO foveal cone density data by Wang *et al*.<sup>7</sup> The average peak density from the Wang *et al* data is  $168.047 \times 10^3$  cones/ $\text{mm}^2$  (ranging from  $123.611 \times 10^3$  to  $214.895 \times 10^3$ ). The mean peak cone density of these three subjects with MacTel was  $80.7 \times 10^3$  cones/ $\text{mm}^2$ , lower than the minimum peak density reported by Wang *et al*. Two-way ANOVA shows that cone density within  $0.5^\circ$  in patients with MacTel is significantly lower than the normal population ( $p < 0.05$ ).



**Figure 1** (A) The clinical fundus images of subject 1 in the less-affected eye. (B) Cone montage around the foveal centre (the white square in panel A). (C) Cone density map, white cross shows the peak cone density (S: superior, I: inferior, T: temporal and N: nasal). (D) Cone labelling, cone images correspond to the regions highlighted with a dashed box in panel C. (E) FFA image of subject 1 in the affected eye (OD) showing temporal leakage. (F) FFA image of subject 1 in the less-affected eye (OS) showing no leakage.



**Figure 2** The measured cone packing density from the foveal centre to about  $0.8^\circ$  at all four meridians. Curves replotted from Wang's study are depicted as dashed lines (maximum, mean and minimum cone densities).

Figure 2 shows the measured cone packing density from the foveal centre to about  $0.7^\circ$  at all four meridians. Curves replotted from Wang *et al's*<sup>7</sup> study are depicted as dashed lines (maximum, mean and minimum cone densities). Compared with the AOSLO foveal cone data from normal subjects, cone density at perifoveal area (within  $0.5^\circ$  radius) was lower in the patients with MacTel.

## DISCUSSION

### Earliest microscopic change in MacTel is loss of foveal cones

MacTel has traditionally been considered primarily a vascular disease affecting juxtafoveal retinal capillaries with macular oedema and exudation being the main cause for visual loss in these patients. However, Ooto *et al*<sup>2</sup> recently reported AOSLO findings of dark regions in the extrafoveal cone mosaic and decreased cone density in those areas associated with decreased vision in a cohort of patients with type 2 MacTel. Paunescu *et al*<sup>8</sup> and Barthelmes *et al*<sup>9</sup> also reported optical coherence tomography (OCT) results demonstrating that the photoreceptor layer was disrupted in patients with MacTel. The patients imaged in this study were at a much earlier stage in the disease process than those reported on in these previous imaging studies with no or only subtle clinical changes in the eyes we examined. Our results suggest that at even this very early stage of MacTel, peak cone density is already lower than the minimum peak density observed for normal eyes. However, just outside the foveal centre, at  $0.5^\circ$ , these

patients fall within the normal range (contrary to the report of Ooto *et al*<sup>2</sup>). It is also possible that with such a small number of patients, there is insufficient statistical power to detect a difference in the parafoveal retina. It should be noted that it is unclear if these patients had reduced cone density from birth or if it decreased gradually over time. Follow-up imaging needs to be performed to observe cone density change overtime both at the foveal centre and parafoveal retina to examine the rate and regional variability of progression of both photoreceptor and vascular changes.

Charbel Issa *et al*<sup>10</sup> found decreased macular pigment (MP) in patients with MacTel. They suggested that the reduced MP may be due to either a primary loss of MP from defective trafficking or storage of MP or, a secondary loss due to pathology of the anatomical structures involved in the process of MP accumulation.<sup>11</sup> Since MP exists in the axons of the cone photoreceptors in the central retina,<sup>12</sup> the existence of fewer cones in the central retina provides an alternative explanation for the observed decrease in MP. A recent study<sup>13</sup> showed Müller cell reduction in patients with MacTel type 2. Müller cells play an important role in photoreceptor development and survival.<sup>14</sup> It has been reported that a targeted disruption of Müller cell metabolism adversely affected the assembly of the photoreceptor outer segment membrane and photoreceptor dysmorphogenesis can result from the compromise of Müller cells.<sup>15</sup> Because of poor preservation of photoreceptors in all the samples, they could not determine if there was



a reduction of cone numbers in the MacTel fovea. It is possible that the reduced cone photoreceptor density we observed in patients with MacTel is related to a depletion or dysfunction of Müller cells.

High-resolution imaging studies provide unprecedented microscopic disease characterisation in the living eyes of patients that may be very valuable for better understanding rare diseases such as MacTel. The reduced foveal cone density in the clinically less-affected eyes in patients with asymmetric MacTel that we observe here suggests that future studies with high-resolution imaging capabilities should not only focus on the vasculature, but also on the photoreceptors in the fovea. It is possible that foveal cone photoreceptor loss may precede the classic obvious vascular changes observed at later stages in MacTel, or the foveal cone loss may happen concurrently with the vascular changes.

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