Optical Coherence Tomography Biomarkers of Photoreceptor Degeneration in Retinitis Pigmentosa

Yuting Gong
Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong
Honghe Xia
Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong
anlin zhang
Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong
LiJia Chen
The Chinese University of Hong Kong Department of Ophthalmology and Visual Sciences
Haoyu Chen (drchenhaoyu@gmail.com)
Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong

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Abstract

Purpose: Several parameters on optical coherence tomography (OCT) have been suggested as biomarkers for photoreceptor degeneration in retinitis pigmentosa (RP). This study is to investigate which OCT parameters can serve as the earliest biomarkers in RP.

Methods: OCT line scans of the horizontal meridian were conducted in 22 eyes of 22 RP patients and 30 eyes of 30 healthy controls. Longitudinal reflectance profiles were obtained using ImageJ at every 5 pixels. The following parameters on OCT were quantitatively measured: 1) relative optical intensity (ROI) of ellipsoid zone (EZ) and interdigitation zone (IZ); 2) thickness of outer nuclear layer (ONLT), photoreceptor (PRT), inner segment (IST) and outer segment (OST). The variations of these parameters across different regions were analyzed.

Results: From fovea to peripheral retina, all the OCT biomarkers declined before disappeared, except IST and IZ-ROI. There was no identifiable declining zone for the IST and IZ-ROI between the normal and disappeared zones. The earliest biomarker was the shortening of OST and reduced IZ-ROI, followed by the shortening of PRT, EZ-ROI, then IST, and finally, ONLT. All these biomarkers had significant correlations with best-corrected visual acuity, except ONLT.

Conclusion: In retinitis pigmentosa, EZ-ROI, IZ-ROI, PRT, OST, IST and ONLT are valuable biomarkers of photoreceptor degeneration. OST and IZ-ROI may serve as the earliest biomarkers.

Introduction

Photoreceptor degeneration is an important cause of visual impairment in many diseases, such as inherited retinal degeneration, retinal detachment, diabetic retinopathy and age-related macular degeneration.[1-5] Optical coherence tomography (OCT) provides high-resolution visualization of the cross-sectional morphology of the retina.[6] There are four hyperreflective bands on OCT images of a normal retina, including external limiting membrane (ELM), photoreceptor inner segment ellipsoid zone (EZ), interdigitation zone (IZ) and retinal pigment epithelium (RPE). In patients with photoreceptor degeneration secondary to various causes, disruption of EZ and IZ are important biomarkers.[7-9] With advanced image analysis techniques, some parameters of the photoreceptors can be measured. In our previous study, we demonstrated in retinitis pigmentosa (RP) patients that the relative optical intensity (ROI) of EZ and IZ declined in the regions where it remained intact on B scan[10]. Furthermore, the EZ-ROI at the fovea was correlated with visual acuity. Besides, the shortening length (or thickness) of the photoreceptors and its inner and outer segments were also found to suggest the damage of photoreceptors.[11, 12] In addition, the reduced thickness of the outer nuclear layer (ONL) was found in severe photoreceptor degeneration.[13] However, it remained unknown which is the earliest identifiable biomarker for photoreceptor degeneration.

Retinitis pigmentosa is a group of genetic disease characterized by progressive photoreceptor damage from peripheral retina to macula.[14] There are three zones with different stages of photoreceptor lesion

on the retina of RP patients at the early phase, i.e., a relatively healthy zone at the fovea, a severely affected peripheral zone, and the transition zone between them.[14, 15] There are various degrees of degenerated photoreceptors presented on OCT images, allowing us to analyze the progress of photoreceptor degeneration with cross-sectional data. In this work, we quantitatively analyzed multiple OCT parameters in different retinal areas of RP patients, with a view to identify the earliest biomarkers of photoreceptor degeneration.

Subjects And Methods

Study subjects

This is a retrospective study. It was approved by the Institutional Review Board of Joint Shantou International Eye Center, Shantou University and the Chinese University of Hong Kong. All procedures adhered to the tenets of the Declaration of Helsinki. Because of the retrospective nature of the study, informed consent was waived.

Totally 22 RP patients and 30 healthy controls were included in this study. The participants have been described in our previous study.[10] The diagnosis of RP was based on clinical history, ophthalmoscopy, and electroretinography. The controls were free from ocular diseases except cataract, conjunctivitis, dry eye or refractive error. All participants received OCT examination by Zeiss Cirrus HD-OCT 4000. Subjects with the following conditions were excluded: 1) the EZ was disrupted at fovea on OCT; 2) subjects with a history of ocular trauma or intraocular surgery; 3)) spherical equivalent greater than ±6.0 diopters; and/or 4) the signal strength of the OCT images was less than 4. Best-corrected visual acuity (BCVA) was measured using Snellen visual chart and was converted into LogMAR for statistical analysis.

OCT images

Every participant received examination with Zeiss Cirrus HD-OCT 4000 by 5-line mode (Carl Zeiss Meditec, Dublin, CA). The length of each line scan, i.e., B scan, was 6 mm. If both eyes of the same subjects were examined, the one with better image quality scores was inlucded in the data analysis. The grayscale images of B scan passing through foveola of each selected eye were exported from Cirrus 4000 with default values.

Image analysis

The grayscale images were imported into Image J (National Institutes of Health, Bethesda, MD). The size of each images was 750 x 500 pixels. The images were rotated 90-degree counter clockwise to make the external limiting membrane at the left and the RPE at the right. Then longitudinal reflectivity profiles (LRPs) were obtained from the regions of interest with 5 pixels width and 110 pixels length across the full-thickness retina and demonstrated the optical intensity as the function of depth. The region of interest was first set at the fovea and then moved to nasal and temporal retina continuously. Thus each B scan image had 150 LRPs to demonstrate the optical intensity from nasal to temporal retina.

For a healthy retina, the LRPs usually have four successive peaks at the coordinates corresponding to the ELM, EZ, IZ, and RPE respectively. The peak value is recorded as the optical intensity of each band.[16] In RP patients, there may be a defect of IZ, EZ, or ELM peaks. We recorded all peak values and their coordinates on the LRPs.

EZ-ROI and IZ-ROI were calculated as dividing the peak of EZ and IZ, respectively, by the mean reflection of the whole retina at the same position. The inner limit of the retina was defined as where the slope is maximal between the internal limiting membrane and the posterior vitreous cortex. Similarly, the position with a maximal slope between the RPE and the choriocapillaris defined the outer limit of the retina. The mean value that all dots on an LRP between the inner and outer limits was the average intensity of the whole retina.

The photoreceptor thickness (PRT) was defined as the distance between the peak of ELM and RPE. The inner segment thickness (IST) and outer segment thickness (OST) were defined as the distance from ELM peak to EZ peak, and EZ peak to RPE peak, respectively (Figure 1). The thickness of the outer nuclear layer (ONLT) was defined as the distance from the interface of the outer plexiform layer (OPL) and ONL, the position with a maximal slope between the two layers, to ELM, or to the interface of ONL and RPE if ELM disappeared in PR patients. The transverse IZ, EZ, and ELM length were the distance between the point where bands disappear at the temporal and nasal side. If the bands existed beyond the scanning window, only the length within the window was calculated.

Data analysis

For data analysis, a new coordinate system was established (Figure 2 B-G), with the fovea representing the original point and the distance between the point of interest and the fovea being the horizontal axis. Retinal areas nasal to the fovea were defined as within the positive half, and temporal ones in negative half. Then the vertical axis represented the quantitative measurement of the biomarkers.

The mean and 95% confidence interval (95% CI) of the intensity of the biomarkers at each point in the control group served as the normal range. Then the biomarkers of each RP patient were compared to the corresponding normal ranges. Besides, the averages of these biomarkers within the central 1-mm-wide region were calculated and compared between RP and controls using independent t test or Mann-Whitney U test. The correlations between these parameters and BCVA were analyzed using Spearman correlation. For comparison between groups, a P value of <0.05 was defined as statistically significant.

Results

Totally 22 patients and 30 controls were included in this study. There was no significant difference in age and gender between the two groups, whilst the BCVA and signal strength of OCT images were significantly better in controls than in RP patients (Table 1).

All of 22 eyes of the RP patients had preserved EZ and ELM at the fovea, but only eight patients had preserved IZ at the fovea. The transverse IZ length (57.27±100.28 pixels) was consistently shorter than the transverse length of EZ (248.41±159.09 pixels) in the same eye ($P < 0.001$), and the transverse EZ length was always shorter than the ELM length (355.68±152.42) in the same eye ($p < 0.001$).

The variation of the OCT biomarkers in patients followed a similar pattern. The values of EZ-ROI and IZ-ROI, PRT, IST and OST can be normal or reduced at the fovea (Figure 3). In contrast, ONLT can be increased (Figure 2G), normal or reduced at the fovea. When moving peripherally, the values of the biomarkers decreased and even disappeared (Figure 2 and Figure 3). For EZ-ROI, PRT, OST and ONLT, there was always a declining zone before they disappeared. However, there can be no declining zone for the IST (Figure 4) and IZ-ROI (Figure 2C) between the normal and disappeared zones.

By comparing the locations where these biomarkers varied in all participants (Figure 3), we found that the earliest biomarker was the reduced or disappeared IZ-ROI in most cases, except in two cases (RP2 and RP6) (Figure 5), in which reduced OST was the earliest biomarker. Then PRT began to decline eccentrically or at the same location as OST declined. The disappearance of IZ usually occurred after the reduction of IZ-ROI, OST and PRT (Figure 2). The next change of biomarker was the EZ-ROI reduction, and finally IST and ONLT reduction.

All the quantitative OCT biomarkers except ONLT within the foveal 1 mm region were statistically lower in RP patients than in controls (Table 2). All the OCT biomarkers except ONLT were significantly correlated with BCVA (LogMAR) in the RP patients (Table 2). The strongest correlation was detected between IST and BCVA ($r = -0.653$, $p= 0.001$). The correlation coefficient was -0.534, -0.593, -0.647, -0.480, -0.476 and -0.559 for EZ-ROI, IZ-ROI, PRT, OST, EZ length and IZ length, respectively (all $p < 0.05$). Moreover, these biomarkers were significantly correlated with each other, except the correlation of ONLT with IZ-ROI or IZ length (Table 3).

Discussion

In this work, we evaluated the length and optical intensity of outer retina bands, as well as the thickness of photoreceptor segments and ONL in RP patients and controls. The transverse lengths of ELM, EZ and IZ were significantly shorter in RP patients than in controls. All biomarkers, except IST and IZ-ROI, varied from the fovea to peripheral retina followed a same pattern that they declined before disappeared. Besides ONLT and ELM length, the biomarkers were all related to BCVA. These biomarkers followed a coincident order in the progression of RP that the IZ-ROI or OST declined first, followed by the reduction of PRT, EZ-ROI, and finally the IST and ONLT.

On OCT B scan, disruption of the hyperreflective bands is the sign commonly used to identify photoreceptor degeneration. [7-9] In our study, all RP patients had transverse IZ length shorter than the transverse EZ length, while the latter is shorter than the ELM length. Our study suggested that the IZ disruption should be earlier than EZ and ELM. This result is consistent with those in previous reports.[7, 17, 18] However, it is noteworthy that IZ may be indistinct at perifoveal regions in some healthy controls. It

has been reported that 6 of 26 control subjects displayed an interrupted IZ.[8] Therefore, the absence of IZ band at the perifoveal region may not be a necessary indication of pathology.

Compared to the disruption of the hyperreflective bands at the outer retina, quantitative measurement of the thickness and optical intensity of the photoreceptors are earlier biomarkers of photoreceptor degeneration. [10-12] Our study found that these biomarkers declined before disappearing eccentrically, except IST and IZ-ROI. Hood and colleagues reported that the OST and ONLT gradually declined at the transition zone between normal and severely affected areas in RP.[14] Our results on OST and ONLT were consistent with Hood's report.

By comparing the locations of all biomarker variation, we found that the IZ-ROI and OST were the earliest ones which declined in photoreceptor degeneration process, followed by the PRT thinning, EZ-ROI decreasing and finally the IST and ONLT thinning. This finding is consistent with photoreceptor degeneration starting from the outer segment to the inner segment in RP.[19] The earliest histopathologic change is reportedly the shortening of outer segments in rods of RP.[20] On OCT, the shortening of the outer segment of rod occurred before ONL thinning and EZ disappearing in Usher syndrome.[21] Our study suggested that besides from reduced OST, decreased or disappeared IZ-ROI could also be the earliest biomarker. This finding would help us to identify photoreceptor degeneration at an earlier stage.

The ONL thinning at the fovea was found more frequently in RP patients with a more advanced stage.[7] However, there were several patients having ONL thickened at the fovea in the current study. This may be a consequence of retinal remodeling in photoreceptor degeneration.[18]

Except for ONLT and the transverse ELM length, we found that all the other biomarkers had a significant correlation with BCVA. In the literature, there were several reports of the association of OCT biomarkers with visual acuity, such as the presence of EZ at fovea [19], length of the IZ,[17] thickness of outer segments and full thickness of photoreceptor,[22-24] and optical intensity of EZ.[10] In our work, the mean IST within the central 1-mm-wide retinal area had the greatest correlation with BCVA among these metrics. Considering the inner segment ellipsoid of photoreceptor consisting of a thick density of mitochondria, which provides energy,[25] its structural integrity and intact function may be valuable to preserve visual function.

We recognized some limitations in this work. First, the OCT image was not flat in some patients, and the peak of EZ on LRPs might consist of the EZ and neighboring structure. We tried to minimize this bias by reducing the width of the region of interest to 5 pixels. Second, the band between OPL and ELM was consisted of two parts that the upper part was the Henle fiber layer and the inferior part the ONL on OCT. [26] We did not differentiate them. Third, this is a cross-sectional study. Further longitudinal studies are needed to verify our results.

The transverse length and optical intensity of EZ and IZ, as well as thickness of photoreceptor IS and OS are all valuable biomarkers indicating photoreceptor degeneration in RP. The IZ-ROI and OST are likely to

be the earliest change in RP, and PRT and optical intensity can serve as the earlier biomarkers than EZ length on OCT.

Declarations

Acknowledgements: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of patients and controls

		RP patients	Control group	P value
N		22	30	
Age (year)		44.6±17.3	39.9±18.3	0.354*
Gender	Male	9 (40.9%)	14 (46.7%)	0.680#
	Female	13 (59.1%)	16 (53.3%)	
OCT quality		6.36±1.53	8.53±1.20	<0.001**
BCVA (LogMAR)		0.50±0.68	0.04±0.10	<0.001**

* Independent sample t-test # Chi-square test ** Mann-Whitney U test

Table 2. OCT biomarkers correlated with BCVA in RP patients and comparison between RP and controls.

	Comparison			Correlation with BCVA	
	RP	Controls	t-test *p*	r	Spearman *p*
ROI of EZ	1.51±0.43	1.95±0.11	<0.001	-0.534	0.011
ROI of IZ	0.58±0.82	1.98±0.17	<0.001	-0.593	0.004
PRT (pixel)	14.19±3.74	20.85±0.72	<0.001	-0.647	0.001
OST (pixel)	7.52±3.17	12.92±0.59	<0.001	-0.480	0.024
IST (pixel)	5.90±1.65	7.90±0.38	<0.001	-0.653	0.001
ONLT (pixel)	23.21±7.16	23.56±6.17	0.856	-0.312	0.157
IZ length (pixel)	57.27±100.28	710.33±85.54	<0.001	-0.559	0.007
EZ length (pixel)	248.41±159.09	750.00	<0.001	-0.476	0.025
ELM length（pixel）	355.68±152.42	750.00	<0.001	-0.234	0.296

Table 3. Correlations metrics between the biomarkers

	ROI of EZ	ROI of IZ	PRT	OST	IST	ONLT	EZ length	IZ length
ROI of EZ	1.000	0.519*	0.871***	0.809***	0.893***	0.619**	0.919***	0.604**
ROI of IZ	0.519*	1.000	0.743***	0.761***	0.504*	0.359	0.539*	0.948***
PRT	0.871***	0.743***	1.000	0.961***	0.852***	0.668**	0.854***	0.788***
OST	0.809***	0.761***	0.961***	1.000	0.740***	0.632**	0.793***	0.810***
IST	0.893***	0.504*	0.852***	0.740***	1.000	0.603**	0.846***	0.552**
ONLT	0.619**	0.359	0.668**	0.632**	0.603**	1.000	0.624**	0.362
EZ length	0.919***	0.539*	0.854***	0.793***	0.846***	0.624**	1.000	0.629**
IZ length	0.604**	0.948***	0.788***	0.810***	0.552**	0.362	0.629**	1.000

*P<0.05 **P<0.01 ***P<0.001

Figures

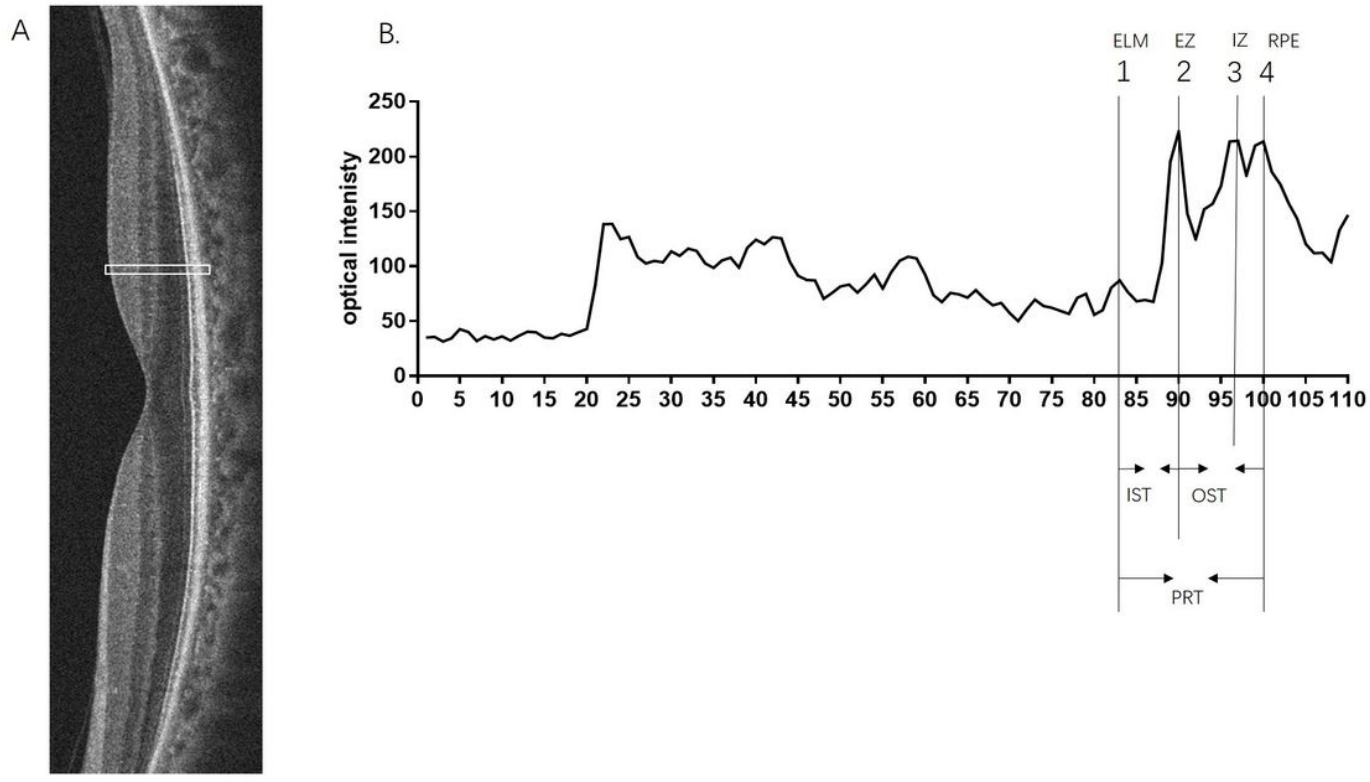

Figure 1

Measurement of OCT biomarkers in a retinitis pigmentosa patient. A. The OCT image an RP patient. B. The longitudinal reflectance profile of the retina corresponding to the white rectangle. The four vertical lines from left to right indicate the location of the peaks of external limiting membrane (ELM), ellipsoid zone (EZ), interdigitation zone (IZ) and retinal pigment epithelium (RPE) respectively. Inner segment thickness (IST) was defined as the distance between lines 1 and 2. Outer segment thickness (OST) was defined as the distance between lines 2 to 4. Photoreceptor thickness (PRT) was defined as the distance between lines 1 and 4.

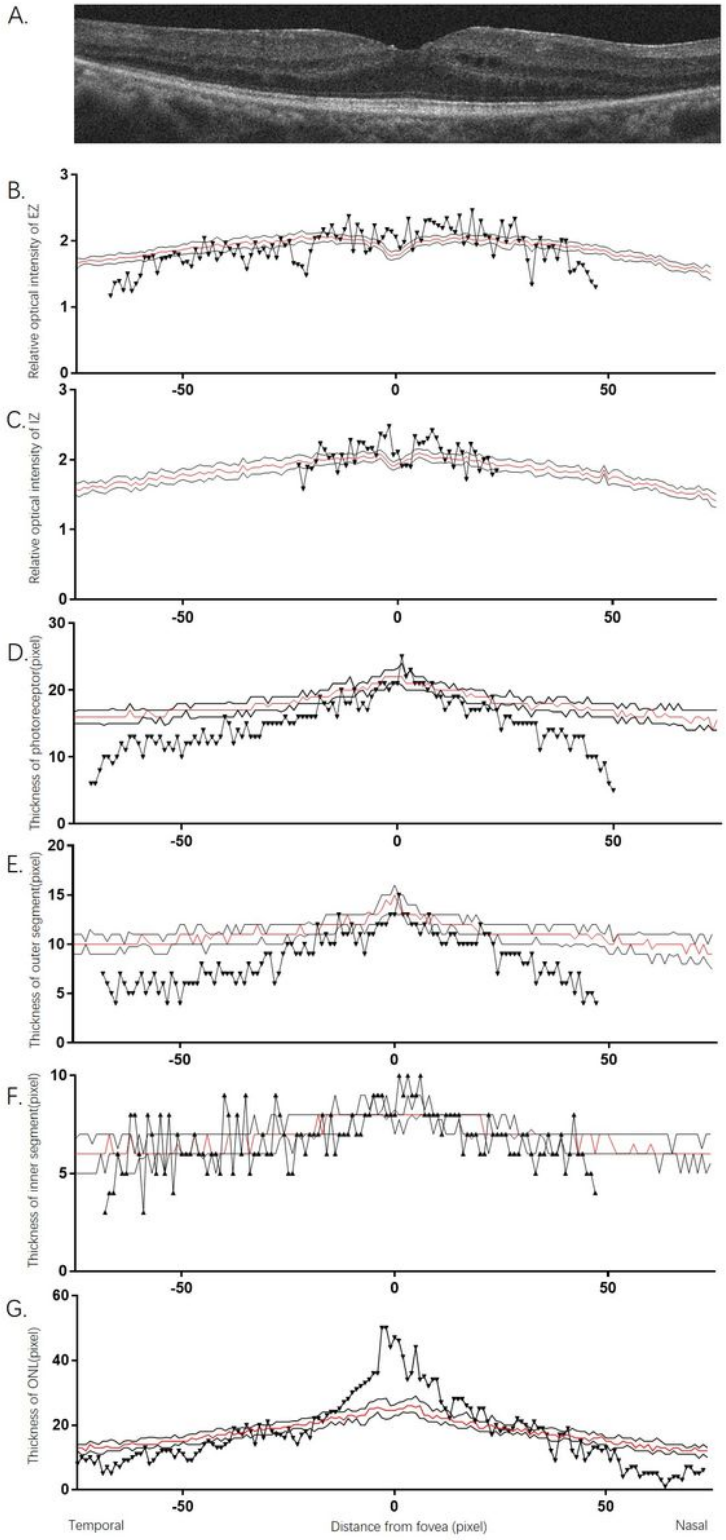

Figure 2

The thickness and optical intensity analysis of outer retina in an RP patient (RP2). A. The horizontal OCT B-scan image passing through the fovea. For the coordinates in B to G, the original points represent the fovea, with the distance from the fovea being the horizontal axis of which nasal seated within positive half and temporal was in negative half. The red curves represent the mean and the thin black curves

represent the 95% confident interval of 30 healthy controls. The thick black lines with triangles represent the values of the parameters in A.

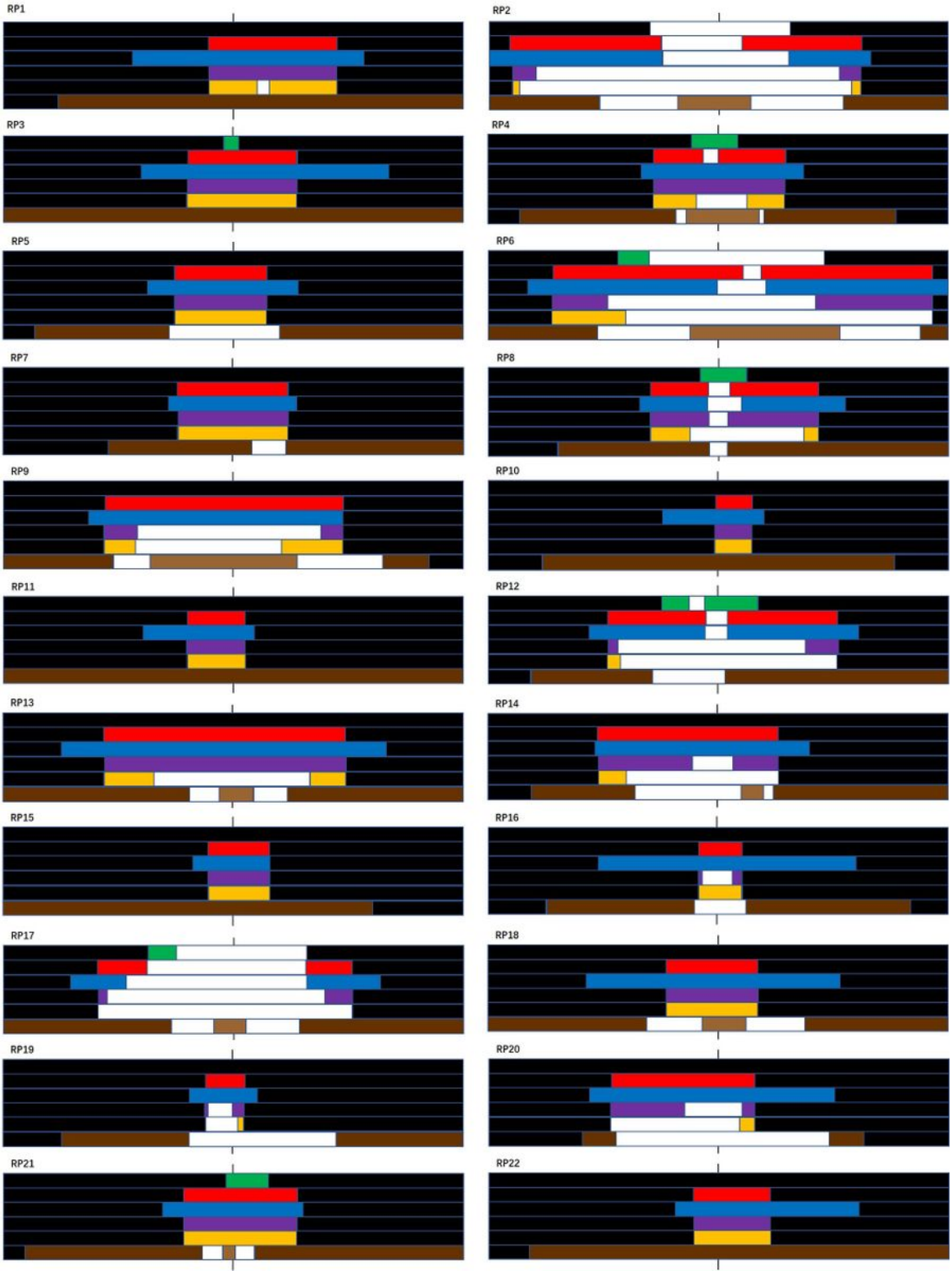

Figure 3

Spatial distribution of the changes of OCT biomarkers in 22 individual patients. The thin black lines indicate the position of fovea. There are six bars with different colors representing each biomarker. From up to down, they are interdigitation zone relative optical intensity (green), outer segment thickness (red),

photoreceptor thickness (blue), ellipsoid zone relative optical intensity (purple), inner segment thickness (orange), and outer nuclear layer thickness (dark brown). For each bar, white represents normal zone and the black depicts the complete loss of the biomarker, while colors represent the declining zone. The light brown zone at the bottom bar showing the region with thickened outer nuclear layer.

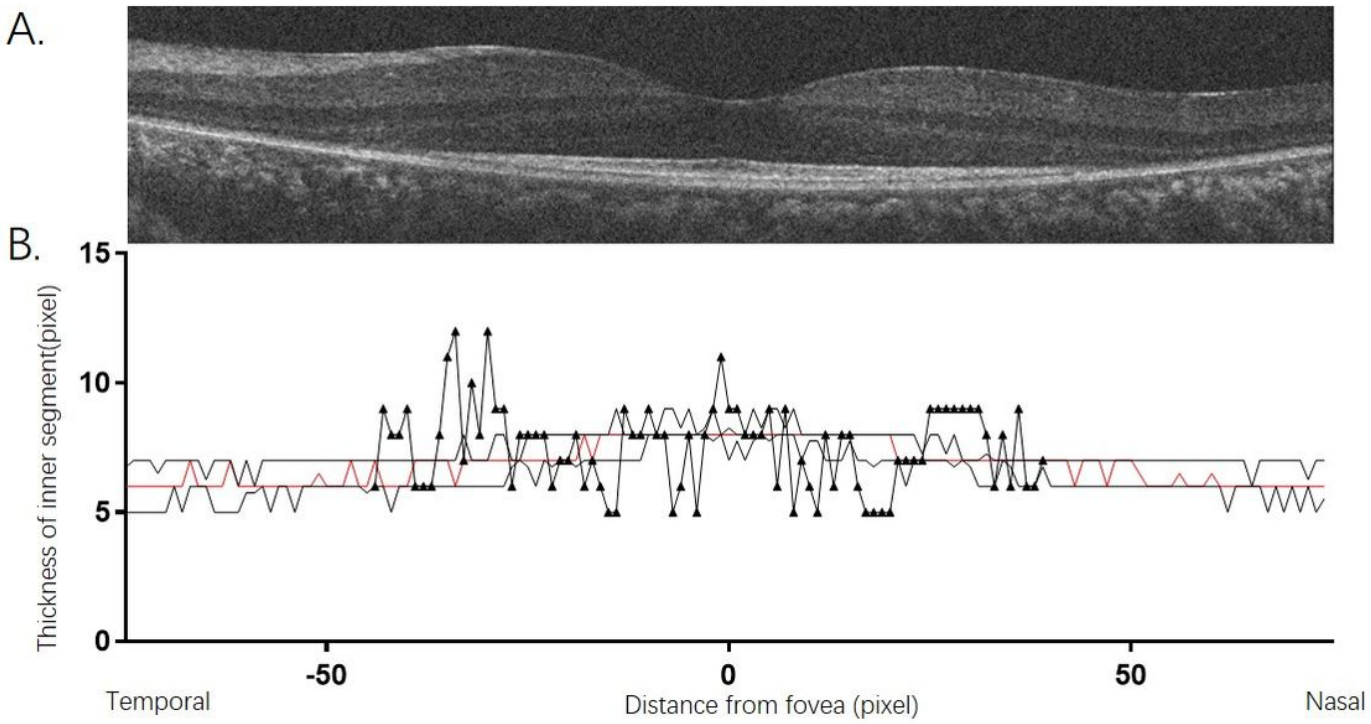

Figure 4

NO inner segment thickness declining zone between normal and disruption zone in an RP patient (RP17). A. The horizontal OCT B-scan image passing through the fovea. B. Inner segment thickness analysis. The original point represents fovea and the horizontal axis represents the distance from fovea with nasal and temporal being in positive and negative half respectivily. The red curves represent the mean and the thin black curves represent the 95% confident interval of 30 healthy controls. The thick black lines with triangles represent the inner segment thickness of the OCT image in A.

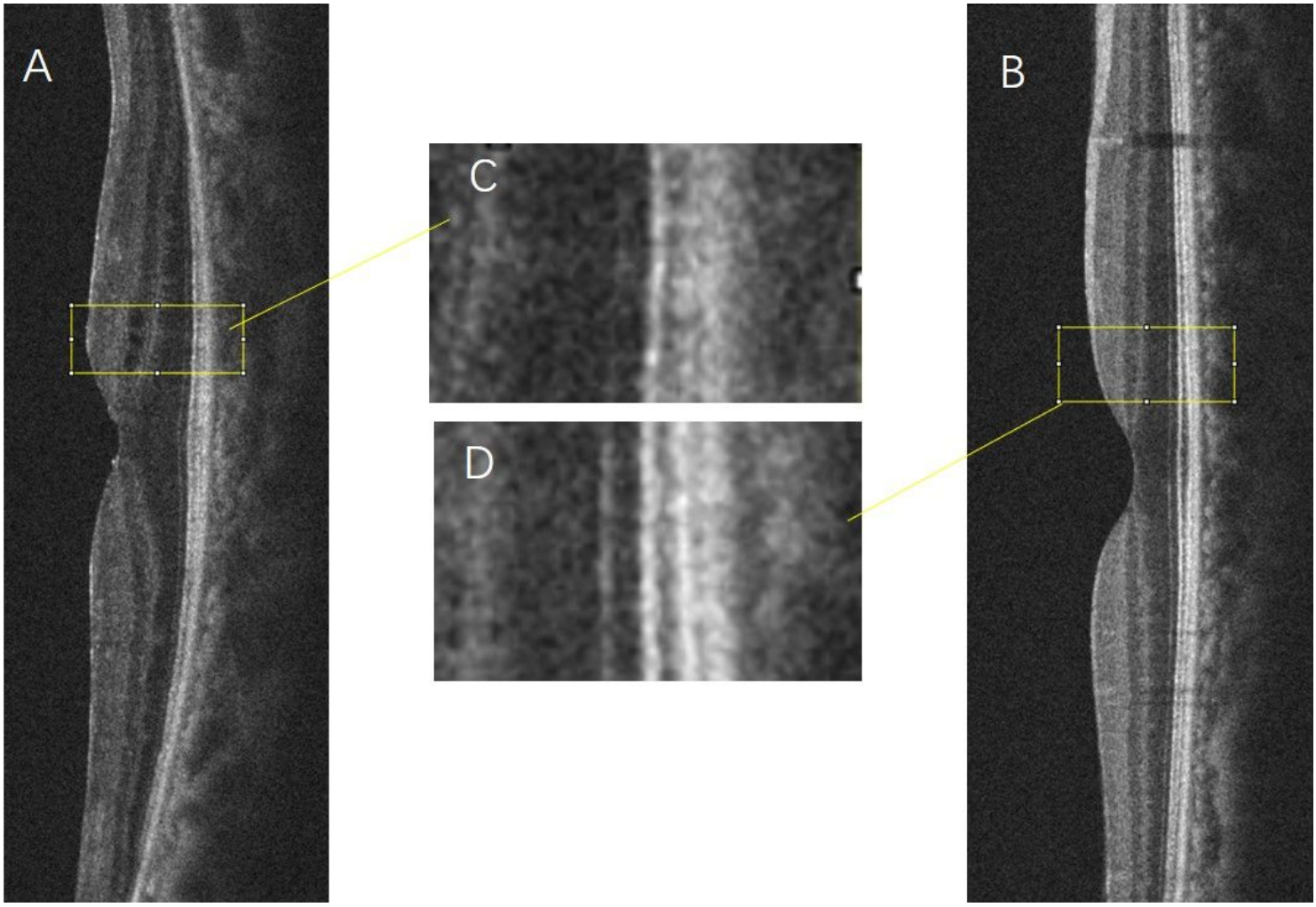

Figure 5

Magnified OCT images demonstrating the earliest biomarker is reduced outer segment thickness. A. the OCT images of RP2. B. OCT image of a healthy participant. C and D are the magnified images of the yellow rectangle region in A and B. In C, only outer segment thickness decreased below the normal range, while all the other biomarkers remain normal.