Correlations between annual progression of retinal function and retinal microstructures in eyes with retinitis pigmentosa

（網膜色素変性の病状進行過程における視機能と網膜外層構造の関係）

千葉大学大学院医学薬学府

先端医学薬学専攻

（主任：山本　修一教授）

千葉　晃大

ABSTRACT.

Objectives: To investigate the relationship between the visual functions and the microstructures of the photoreceptors in eyes with retinitis pigmentosa (RP).

Method: The medical records of patients with typical RP were reviewed. The best-corrected visual acuity (BCVA) was recorded, and the lengths of the intact external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ) were measured by spectral-domain optical coherence tomography. The retinal sensitivity was measured by Micro Perimeter-1. The correlations among these factors were determined by generalized estimating equation regression analysis because of the inter-eye correlations.

Results: Forty-six eyes of 24 patients who were examined over a mean follow-up period of 3 years were studied. The annual changes in the retinal sensitivity (p = 0.0035), and the lengths of the EZ (p = 0.037) and IZ (p = 0.0033) were significantly correlated with their baseline values. The annual changes in the retinal sensitivity was significantly correlated with the EZ at the baseline (p = 0.020).

Conclusions: A slower decrease in the retinal sensitivity was associated with a poorer retinal sensitivity and a shorter EZ at the baseline, and a slower decrease of the EZ and IZ were associated with a shorter EZ and IZ at the baseline.

Introduction

Retinitis pigmentosa (RP) is an inherited retinal disorder that is associated with progressive degeneration of the photoreceptors and subsequent irreversible reduction of vision. RP affects approximately 1 in 4000 individuals worldwide, and RP patients typically present with night blindness followed by a constriction of the visual fields and severe visual impairment and blindness [1, 2]. Genetic counseling and instructions on optimizing the residual vision remain the main methods of managing RP as there are currently few treatments that can stop or reverse the progression of RP [3, 4]. However, there are a number of therapeutic trials for RP such as gene- [4], drug- [5], and cell-based therapy [6]. Therefore, determining the natural course of the degeneration of the retinal structure and visual function in eyes with RP is important for determining the effectiveness of any type of therapy.

Earlier studies have reported that there are significant associations between the visual function and several structural biomarkers, such as the thickness of the outer nuclear layer [7], the integrity and length of the external limiting membrane (ELM) [8, 9], the ellipsoid zone (EZ) [7–12], and the interdigitation zone (IZ) [9]. Cabral et al. [13] reported that an intact length of the EZ of more than 3000 μm was significantly associated with a faster decrease in the length of the EZ in RP patients. On the other hand, Hagiwara et al. [9] reported that the lengths of the ELM, EZ, and IZ were significantly correlated with the visual acuity and retinal sensitivity. In addition, they reported that the lengths were correlated with each other, and the IZ was the first microstructure to become disrupted followed by the EZ and finally the ELM. In spite of these early findings, the relationship between the decrease in retinal sensitivity and lengths of the ELM and IZ has not been definitively determined.

Thus, the purpose of this study was to determine whether there are significant correlations between the decrease of visual function and the changes in the microstructures of the retinal outer layer determined by spectral-domain optical coherence tomography (SD-OCT) in eyes with RP.

Materials and Methods

This was a review of the medical records of patients with typical RP whose best-corrected visual acuity (BCVA), retinal tomographic images, and the retinal sensitivity had been recorded for at least 2 years at the Chiba University Hospital. The diagnosis of RP was based on the clinical history, funduscopic appearance, visual field testing, fluorescein angiography, and full-field electroretinograms (ERGs) recorded according to International Society for Clinical Electrophysiology of Vision (ISCEV) standardized conditions. Typical RP was defined as RPs excluding atypical RP, such as sector RP and unilateral RP. PR patients were also excluded from this study if they had high myopia, an epiretinal membrane, macular edema, poor fixation, cataract in the center of the lens that affected the BCVA, and completely present or absent ELM, EZ, or IZ in the measurable range by OCT at the baseline.

We determined the inheritance pattern of the participants from family history.

The BCVA was measured with a Japanese standard Landolt C chart, and the decimal acuities were converted to the logarithm of the minimal angle resolution (logMAR) units for the statistical analyses. The integrity of the microstructures of the photoreceptors were determined by SD-OCT. The SD-OCT images were obtained with the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) from 9-mm horizontal and vertical scans through the fovea (Fig. 1). The average of the horizontal and vertical lengths of the ELM, EZ, and IZ were used for the statistical analyses. The ELM, EZ, and IZ were measured independently by two of the authors (AC and GM). In the event of disagreement, the two graders examined the images together and the final width of the lines was decided. The retinal sensitivity was determined with the Micro Perimeter-1 (MP-1, Nidek Co Ltd, Aichi, Japan) at 24 locations covering the central 10 degrees,and the mean retinal sensitivity of the 24 locations was calculated and used for the statistical analyses (Fig. 2).

For the statistical analyses, the decreases in the BCVA, ELM, EZ, IZ, and retinal sensitivity were defined as the difference between the value at the baseline and the value at the final examination. To examine the progression, the annual decrease or decrease/year was determined, and the progression rate which was defined as the annual decrease/baseline value was calculated. Statistical analysis was performed using the R statistical software package, version 3.4.1. Paired *t*-tests were used to determine the significance of the changes in the values during the observation period. The associations between the baseline values and the annual decrease were determined using the generalized estimating equations (GEE) regression analysis because of the inter-eye correlations. GEE is a statistical approach to the analyses of longitudinal and clustered data that was first introduced in 1986 [14]. The level of significance was set as $p < 0.05$.

Results

Forty-six eyes of 24 patients (7 men and 17 women) were studied. The mean ± standard deviation (SD) age of the patients at the baseline was 56.9 ± 11.7 years. The mean observation period was 36.9 ± 4.7 months. The inheritance pattern was: autosomal dominant, 2 eyes of one patient; autosomal recessive, 4 eyes of 2 patients;, and sporadic, 40 eyes of 21 patients. The clinical findings of the 46 eyes are shown in Table 1. At the baseline, the mean BCVA was 0.0420 ± 0.120 logMAR units, the mean retinal sensitivity was 12.7 ± 4.65 dB, the length of the ELM was 4966 ± 1977 µm, the length of the EZ was 4171 ± 1924 µm, and the length of the IZ was 1576 ± 1111 µm. At the final examination, the mean BCVA was 0.0867 ± 0.165 logMAR units, the retinal sensitivity was 10.1 ± 4.56 dB, the ELM was 4682 ± 1879 µm, the EZ was 3725 ± 1781 µm, and the IZ was 1033 ± 976 µm. There was a significant decrease in the BCVA ($p = 0.0085$, paired *t*-test), the retinal sensitivity ($p < 0.0001$), the ELM ($p < 0.0001$), the EZ ($p < 0.0001$), and the IZ ($p < 0.0001$) from the baseline to the final examination. The mean annual decrease in the BCVA was -0.0149 ± 0.0352 logMAR units/year, the retinal sensitivity was 0.880 ± 0.756 dB/year, the ELM was 90.9 ± 110 μm/year, the EZ was 143 ± 136 μm/year, and the IZ was 172 ± 198 μm/year. The mean annual progress rate in the retinal sensitivity from the baseline was 7.4 ± 7.6 %/year, the ELM was 2.0 ± 2.2 %/year, the EZ was 3.8 ± 3.3 %/year, and the IZ was 12 ± 16 %/year.

The correlations between the annual changes and baseline values of each parameter are shown in Table 2. The decrease in the BCVA was not significantly correlated with the BCVA at the baseline (p = 0.88, GEE). The decrease in the retinal sensitivity was significantly correlated with the retinal sensitivity at the baseline ($Y = 6.20e^{-2} X + 0.102$, p = 0.0035; Fig. 3A). The decrease in the length of the ELM was not significantly correlated with the length at the baseline (p = 0.82), but the decreases in the length of the EZ ($Y = 2.55e^{-2} X + 32.7$, p = 0.037, Fig. 3B) and the IZ ($Y = 9.23e^{-2} X + 24.3$, p = 0.0033, Fig. 3C) were significantly correlated with the baseline values.

The correlations between the annual change of visual function and the baseline values of the different retinal microstructures are shown in Table 3. The lengths of the ELM, EZ, and IZ at the baseline were not significantly correlated with the annual BCVA change (p = 0.53, p = 0.40, p = 0.082, GEE; respectively). The lengths of the ELM and IZ at the baseline were not significantly correlated with the annual changes in the retinal sensitivities (p = 0.47, p = 0.86; respectively), but the length of the EZ at the baseline was significantly correlated with the annual change in the retinal sensitivity ($Y = 1.42e^{-4} X + 0.291$, $p = 0.020$, Fig. 3D).

Discussion

The relationship between the annual progression of BCVA and retinal sensitivity and the lengths of the ELM, EZ and IZ was studied in RP patients. Our findings suggested that a slower decrease in the retinal sensitivity and slower decrease in the lengths of the EZ and IZ were associated with a poorer retinal sensitivity and shorter length of the EZ and IZ at the baseline. In addition, the annual decrease of retinal sensitivity was significantly correlated with the length of the EZ at the baseline. These results suggest that the annual decrease of the retinal sensitivity, EZ, and IZ may differ depending on the baseline conditions.

Cabral et al. [13] reported that the length of the EZ line can be used to detect a progression of the retinal microstructures in RP patients. They reported that the average shortening of the EZ line was 140 µm/year (5.2%), and the progression rates were slower for patients with EZ lines that were ≤ 3000 µm at the baseline. In our study, the mean decrease of the EZ length was 143 µm/year (3.8%), and a shorter baseline length was associated with the slower progression. Thus, our results are in good agreement.

We found that the lengths of not only the EZ but also the IZ and retinal sensitivity were significantly correlated with the degree of their annual progression. Hagiwara et al. [9] reported that the length of the IZ was correlated with the BCVA and retinal sensitivity. In addition, previous studies reported that the IZ contributed more to the degree of reflectance of the photoreceptor mosaic than the EZ in the adaptive optics images in retinal diseases [15–19]. The absence of the IZ in the OCT images could be the earliest sign of a loss of the normal cone mosaics in the adaptive optics images [20]. Thus, there is a possibility that measurements of the IZ will be helpful in the assessment of the photoreceptor in patients with RP.

Several studies have reported there is a significant association between the retinal sensitivity measured by microperimetry and the retinal structure [8–10, 12]. However, to the best of our knowledge, there have not been any reports on the annual progression rate of retinal sensitivities determined by MP-1 in RP patients. MP-1 has been used to determine the retinal sensitivities in patients with macular diseases and correlating the sensitivities with the changes in the ophthalmoscopic appearance of the retina [21, 22]. MP-1 is good method to determine the retinal sensitivities of subjects with unsteady fixation or those who have developed a non-foveal preferred retinal locus. In addition, MP-1 has the advantage of having greater sensitivity to detect the changes in RP patients compared to Humphrey Field Analyzer HFA [23]. Thus, MP-1 may be helpful in assessing retinal sensitivities in eyes with RP.

Our study has some limitations. First, our study examined RP patients only at the limited stage of RP. Neither the early stage patients in whom the degeneration has not reached the posterior pole nor the end stage patients in whom the degeneration has reached fovea at the baseline, were examined. Second, en face OCT images of the retinal and choroidal layers were not examined. Hariri et al. [21] reported that measuring the EZ area in en face OCT images rather than the width on OCT B-scan may a better method to determine the structure-function correlations because the preserved EZ area may be compared more easily with the preserved island of vision from perimetric assessments. Newer OCT techniques such as enhanced depth imaging OCT and swept source OCT will be needed to measure wider areas of the retinal outer layer. Actually, we recently showed that the luminal area and the ratio of luminal/total choroidal area in the inner choroid was significantly correlated with the visual function in RP patients and that the choroidal structures were altered in association with the progression of RP [22]. Another limitation is the genetic heterogeneity of the RP patients studied. This makes the interpretation of the natural progression studies difficult to interpret. In general, the rate of decline in visual function has been attributed to many factors including the gene and type of mutations as well as other genetic and environmental factors [1, 2]. In fact, Cai et al. [23] reported that the progression rate of the EZ length is faster in x-linked RP compared to autosomal-dominant RP. Due to the genetic heterogeneity of RP, further studies on the natural progression in large cohorts and multi-center studies are needed.

In conclusion, the annual decrease in the retinal sensitivity and the length of the EZ and IZ were significantly correlated with their baseline values in patients with RP. In addition, the annual decrease in retinal sensitivity was significantly correlated with EZ at baseline.

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Statement of Ethics

The procedure used in this study was approved by the Institutional Review Board of Chiba University (0314), and they conformed to the tenets of the Declaration of Helsinki. An informed consent had been obtained from the patients at the time of their examinations to use their medical information for research studies. Assurance was provided that the anonymity of each patient would be preserved.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Table 1. Clinical findings of participants.

	Baseline	Final	95% CI	*p* value
BCVA, logMAR units	0.0420 ± 0.120	0.0867 ± 0.165	-0.0773 to -0.0120	0.0085*
Retinal sensitivity, dB	12.7 ± 4.65	10.1 ± 4.56	2.0 to 3.3	< 0.0001*
ELM, µm	4966 ± 1977	4682 ± 1879	172 to 394	< 0.0001*
EZ, µm	4171 ± 1924	3725 ± 1781	317 to 577	< 0.0001*
IZ, µm	1576 ± 1111	1033 ± 976	356 to 729	< 0.0001*
	Annual decrease			
BCVA, logMAR units/year	-0.0149 ± 0.0352			
Retinal sensitivity, dB/year	0.880 ± 0.756			
ELM, µm/year	90.9 ± 110			
EZ, µm/year	143 ± 136			
IZ, µm/year	172 ± 198			
	Progress rate			
Retinal	7.4 ± 7.6			

sensitivity, %/year	
ELM, %/year	2.0 ± 2.2)
EZ, %/year	3.8 ± 3.3
IZ, %/year	12 ± 16

Data are presented as means ± SD. * paired *t*-test. CI, confidence interval; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle resolution; ELM, external limiting membrane; EZ, ellipsoid zone; IZ, interdigitation zone.

Table 2. Association between the annual change and baseline value of each parameter using a generalized estimating equations regression analyses.

	Regression coefficient	Standard error	95% CI	*p* value
BCVA	$-7.13e^{-3}$	$4.70e^{-2}$	$-9.93e^{-2}$ to $8.50e^{-2}$	0.88
Retinal sensitivity	$6.20e^{-2}$	$2.12e^{-2}$	$2.04e^{-2}$ to $1.04e^{-1}$	0.0035
ELM	$1.77e^{-2}$	$1.02e^{-2}$	$-2.28e^{-3}$ to $3.77e^{-2}$	0.082
EZ	$2.55e^{-2}$	$1.22e^{-2}$	$1.48e^{-3}$ to $4.95e^{-2}$	0.037
IZ	$9.23e^{-2}$	$3.14e^{-2}$	$3.08e^{-2}$ to $1.54e^{-1}$	0.0033

CI, confidence interval; BCVA, best-corrected visual acuity; ELM, external limiting membrane; EZ, ellipsoid zone; IZ, interdigitation zone.

Table 3. Association between the annual change of visual function and the baseline retinal microstructures using a generalized estimating equations regression analyses.

	Regression coefficient	Standard error	95% CI	*p* value
BCVA				
ELM	$-1.94e^{-6}$	$3.06e^{-6}$	$-7.95e^{-6}$ to $4.06e^{-6}$	0.53
EZ	$-2.68e^{-6}$	$3.17e^{-6}$	$-8.90e^{-6}$ to $3.54e^{-6}$	0.40
IZ	$7.40e^{-6}$	$4.25e^{-6}$	$-9.41e^{-7}$ to $1.57e^{-5}$	0.082
Retinal sensitivity				
ELM	$5.30e^{-5}$	$7.33e^{-5}$	$-9.07e^{-5}$ to $1.97e^{-4}$	0.47
EZ	$1.42e^{-4}$	$6.11e^{-5}$	$2.2e^{-5}$ to $2.62e^{-4}$	0.020
IZ	$-1.38e^{-5}$	$8.12e^{-5}$	$-1.73e^{-4}$ to $1.45e^{-4}$	0.86

CI, confidence interval; BCVA, best-corrected visual acuity; ELM, external limiting membrane; EZ, ellipsoid zone; IZ, interdigitation zone.

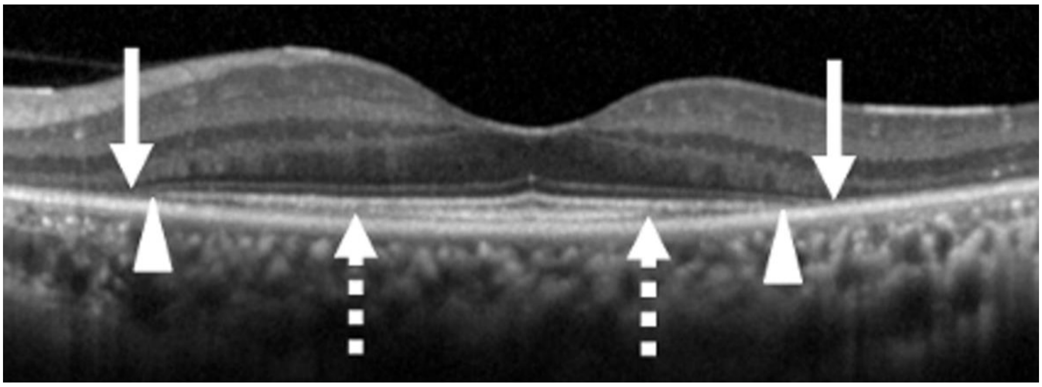

Fig. 1. Optical coherence tomographic image centered on the fovea of a patient with RP. Arrows indicate the ends of the external limiting membrane line, arrowheads indicate the ends of the ellipsoid zone line, and dashed arrows indicate the end of the interdigitation zone.

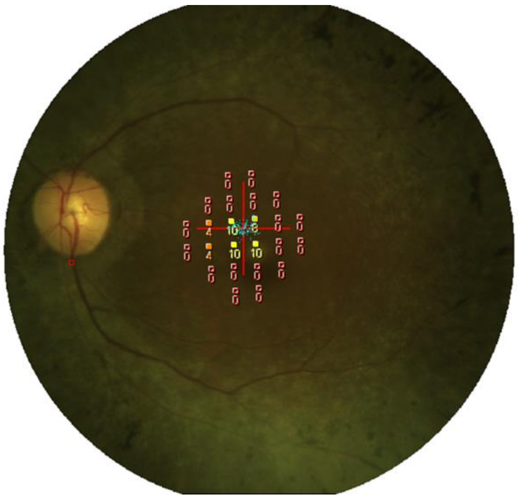

Fig. 2. Micro Perimeter-1 image. A total of 24 stimulus locations covering the central 10° field were tested. The mean retinal sensitivity of the 24 locations is 1.92 dB.

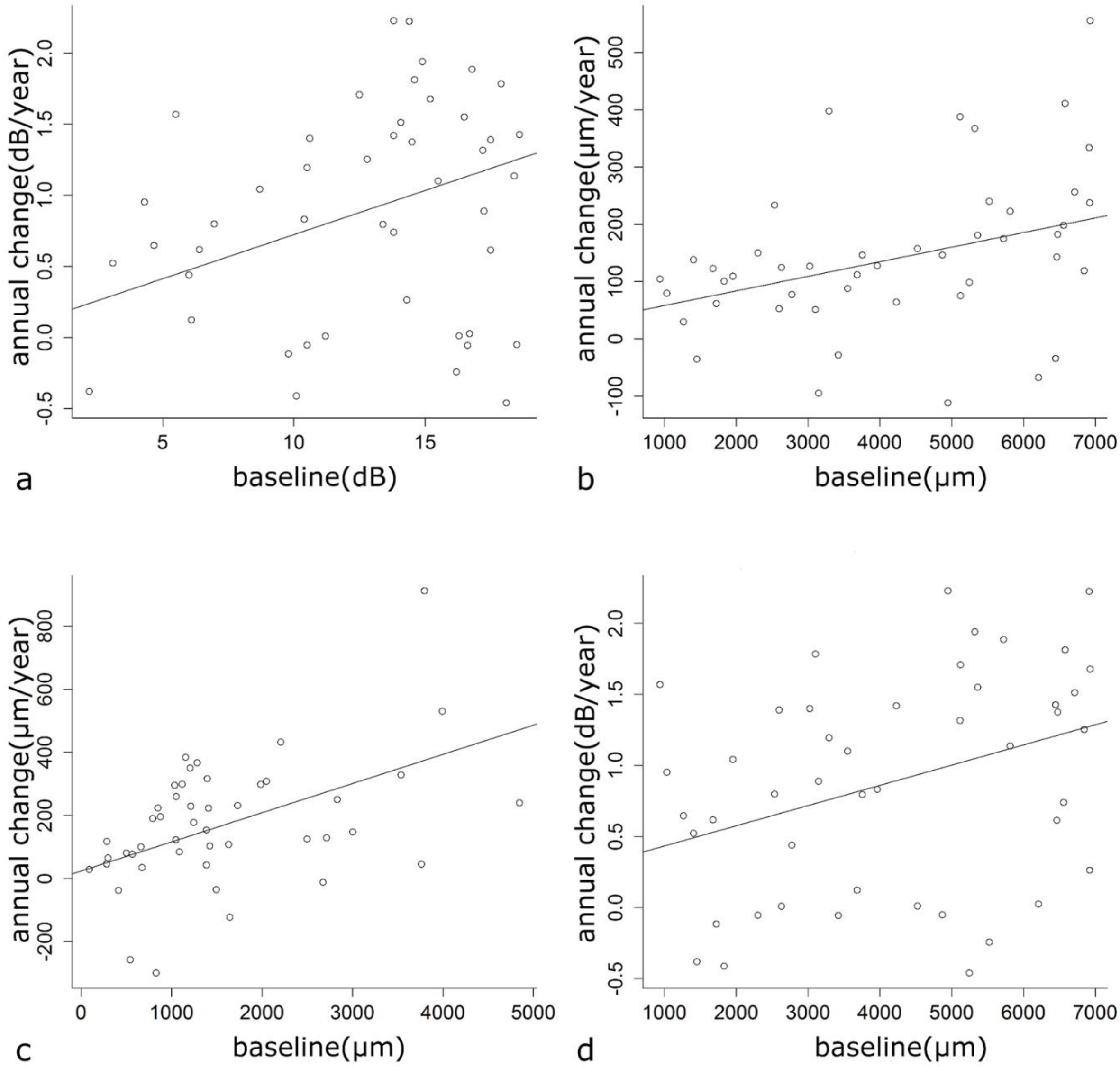

Fig. 3. Generalized estimating equation regression model. (**a**) Retinal sensitivity change/year = 6.20e^{-2} x retinal sensitivity at baseline + 0.102 (p = 0.0035). (**b**) EZ change/year = 2.55e^{-2} x EZ at baseline + 32.7 (p = 0.037). (**c**) IZ change/year = 9.23e^{-2} x IZ at baseline +24.3 (p = 0.0033). (**d**) Retinal sensitivity change/year = 1.42e^{-4} x EZ at baseline + 0.291 (p = 0.02). ELM, external limiting membrane; EZ, ellipsoid zone; IZ, interdigitation zone.