Detection Sensitivity of Retinitis Pigmentosa Progression Using Static Perimetry and Optical Coherencetomography

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Purpose: To compare the detection sensitivities of the progression of retinitis pigmentosa (RP) by automated perimetry to obtain the mean deviation (MD) and total point score and by optical coherence tomography (OCT) to determine the residual ellipsoid zone (EZ) length and thickness of retinal layers.

Methods: Twenty-two eyes of 22 patients with RP who underwent annual automated perimetry (Humphrey Field Analyzer 10-2) and OCT examinations during the same period more than four times were included. Disease progression was evaluated using linear regression analysis with the least-squares method. The disease progression speed and interinspection fluctuations for the different examinations were compared using standardized values. The progression detection ability factor, defined as the average of the least squares divided by the square of annual change, was used to compare the sensitivities of the examinations for detecting the progression of RP.

Results: EZ length showed a high correlation with MD ($R = 0.87; P = 1.12E-07$) at baseline. Disease progression was detected more frequently using EZ length (12/22 eyes) than using MD (3/22 eyes; $P = 0.004$) or central retinal thickness (1/11 eyes; $P = 0.012$). Linear regression using standardized values showed that the EZ length had the fastest annual change, with the smallest least absolute values. EZ length was more sensitive for detecting RP progression than MD, total point score, visual acuity, or central retinal thickness.

Conclusions: EZ measurement was sensitive for detecting RP progression, and the results of this study indicate that EZ length is appropriate for end points in clinical trials.

Translational Relevance: The study provides a basis for conducting future clinical trials.

Introduction

Retinitis pigmentosa (RP) is the most common type of inherited retinal degeneration, with a prevalence of approximately 1 in 4000, for a total of more than 1 million people globally.1 In RP, the loss of photoreceptors leads to night blindness, progressive visual field loss, and visual impairment. Although no therapies have been established yet, several therapeutic trials are ongoing.2,3 Functional examinations, such as visual acuity, contrast sensitivity, and the visual field test, have been commonly used to monitor disease progression in clinical trials for RP, but considerable fluctuations in the results of these subjective tests limit the accuracy of disease progression evaluation.4–6 Although electroretinography is another generally used functional examination, the function evaluated generally diminishes many years before subjective symptoms begin.1 Morphological and objective examinations, such as optical coherence tomography (OCT) and fundus autofluorescence, began to be widely used for monitoring RP within the past decade.7–17 Ellipsoid zone (EZ) length evaluated by OCT has been reported to correlate well with the outcomes of functional evaluations, such as visual acuity, visual field sensitivity, and electroretinography.4–10,13,14,17–19 Retinal layer thickness measured using OCT has also been reported to

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correlate well with the functional evaluations.\textsuperscript{14,18,20} For the evaluation of the progression of a visual field defect, an annual change by linear regression analysis with the least-squares method is widely used.\textsuperscript{21–24}

The sensitivity for detecting progression depends mainly on two factors. First, rapid progressions are easier to detect. Second, more reproducible measurements can detect smaller changes. In light of this, the most sensitive measurement has not been established.

In the current study, we compared the progression speed and the interinspection fluctuations for the measurements with different units by standardizing them. Next, we devised a factor we refer to as the “progression detection ability factor,” which can be used to compare the progression speed and the fluctuation of the measurements regardless of the units of measurement. The visual field examination findings (mean deviation and total point score for automated perimetry), visual acuities, and morphological measurements evaluated by OCT (EZ length and thickness of retinal layers) were compared using standardized values and the progression detection ability factors.

### Methods

#### Study Subjects

This retrospective longitudinal observational study was approved by the Institutional Review Board and Ethics Committee of the Kyoto University Graduate School of Medicine. The study adhered to the tenets of the Declaration of Helsinki.

The clinical records of patients with non-syndromic RP who visited the retinal dystrophy clinic at Kyoto University Hospital between January 2008 and June 2018 were reviewed. The diagnosis of non-syndromic RP was made based on the clinical history and the findings of comprehensive ophthalmologic examinations, including slit-lamp examination, fundus examination, widefield fundus imaging, and electroretinography. Eyes that underwent annual (every 12 ± 1 months) automated perimetry (10-2 Swedish interactive threshold algorithm standard program; Humphrey Field Analyzer [HFA] 10-2) and OCT examinations (using the Spectralis HRA+OCT system; Heidelberg Engineering, Heidelberg, Germany) during the same period for more than four times were included in this study. The exclusion criteria were as follows: age < 20 years, presence of optic nerve diseases or retinal vascular diseases, history of intraocular surgeries other than cataract surgery, undergoing cataract surgeries during the target period of this study, invisible EZ on OCT images at the first examination, or mean deviation (MD) value of HFA 10-2 ≤ −25 dB at the first examination. OCT tests with unreliable outcomes, such as a fixation loss of >20\%, false-positive rate of >15\%, or false-negative rate of >33\%, and the first HFA10-2 examinations were excluded, which accounted for the subject learning effects.\textsuperscript{25} If both eyes of a patient were eligible, only the right eye was included.

#### Analysis of Visual Field Tests and OCT Imaging

The visual field was examined using standard automated perimetry (10-2 Swedish interactive threshold algorithm standard program; HFA 10-2), with Carl Zeiss Meditec software (Dublin, CA). The MD value and the total point score, which is the sum of the visual sensitivities for all measured locations, were analyzed.

The Spectralis HRA+OCT system was used to scan the macula. Horizontal and vertical 30° scans crossing the fovea were used for residual EZ length measurements. The EZ length was measured in a random order using built-in software in the Heidelberg Engineering OCT system (Fig. 1A). The measured values of the horizontal and vertical scans were averaged and used for the analysis. The retinal layer thickness was measured using horizontal scans crossing the fovea. The foveal total retinal thickness (the distance between the inner limiting membrane and choroid/Bruch's membrane), outer nuclear layer (ONL) thickness, and outer segment (OS)+ thickness (the distance between the EZ and choroid/Bruch’s membrane)\textsuperscript{14,18} were measured. Eyes with cystoid macular edema or epiretinal membrane were excluded from the retinal thickness measurements.

#### Evaluation of Disease Progression

The annual rate of change of each value was calculated using linear regression analysis with the least-squares method. For values other than logMAR visual acuity, the detection of disease progression was regarded as significant if the annual change was <0 and if \( P < 0.05 \) was obtained for the linear regression. For logMAR visual acuity, the progression was regarded as significant if the annual change was >0 and if \( P < 0.05 \) was obtained for the linear regression.

The measured values were standardized in order to make the progression speed and the magnitudes of the interinspection fluctuations comparable between measurements with different units: the visual field examination findings (mean deviation and total point score for automated perimetry), visual acuities, and...
morphological measurements evaluated by OCT (EZ length and thickness of retinal layers). The measured values from each patient were standardized using the average and standard deviation of the measured values for each patient. The annual change and the least absolute values of standardized values for each examination were calculated using linear regression analysis with the least-squares method.
Progression Detection Ability Factor

To compare the sensitivities of the examinations for detecting the progression of RP, the progression detection ability factor was devised based on the least-squares method. The progression detection ability factor was derived using the following equation (Fig. 1B):

\[
\text{Progression detection ability factor} = \frac{\text{average of least squares}}{(\text{annual change})^2}
\]

The average of the least squares was divided by the square of the annual change to cancel out the measurement units. For example, in Figure 1, the annual change in the MD detected by linear regression was 0.22 dB/yr. The average of the least squares (d1, d2, d3, and d4) was 0.63 dB² (Fig. 1A).

The progression detection ability factor for the MD was determined using the following equation: average of least squares/(annual change)² = 0.63 dB²/(0.22 dB)² = 13.0. Likewise, the annual change in EZ length was −73.4 μm/yr. The average of the least squares was 14,323 μm² (Fig. 1A). The progression detection ability factor for EZ length was derived using the following equation: average of least squares/(annual change)² = 14,323 μm²/(−73.4 μm)² = 2.66.

The units were canceled out by dividing them, and the different measurements became comparable.

Progression Detection Ability Factor for Hypothetical Examinations

First, the progression detection ability factor was calculated for hypothetical ideal examination findings, which progressed constantly with or without fluctuation. The factor was calculated based on the actual examination values of the subjects included in this study. The progression detection ability factor calculated for hypothetical ideal examination findings that progressed constantly without fluctuation was constant (4.5E-07) regardless of the progression speed (Figs. 2A, 2B) or the actual values (Figs. 2C, 2D). It was the same (4.5E-07) for the various examinations, such as visual field tests and OCT.

Subsequently, examination findings that progressed constantly with constant fluctuations were assumed. The progression detection ability factor was lower for the fast-progressing cases than for the slow-progressing cases (0.3 in Fig. 2F and 1.0 in Fig. 2E, respectively). The factor was also lower for cases with less fluctuation: 16.0 for large fluctuated (Fig. 2G) and 1.0 for less fluctuated (Fig. 2E) cases. The measurements with lower progression detection ability factors were considered more sensitive for detecting RP progression.

Statistical Analysis

Statistical evaluations were performed using commercially available software (SPSS Statistics 20; IBM Corp., Armonk, NY). The χ² test was used to compare the sensitivities of the examinations for the detection of progression. The paired t-test was used to compare the progression detection ability factors for the examinations. Statistical significance was set at P < 0.05. Where applicable, data were presented as median (first quartile–third quartile).

Results

We reviewed the clinical records of patients with RP, and 66 eyes of 33 patients met the inclusion criteria, whereas 24 eyes were excluded from the analyses according to the exclusion criteria. Only the right eye was included when both eyes were eligible. Finally, 22 eyes from 22 patients were included for the analyses.

The baseline clinical characteristics of the patients are summarized in Table 1. The baseline MD and the total point score derived by HFA 10-2 and the EZ length derived from the OCT images were −13.2 dB (−16.3~−10.7), 1323 dB (1150~1529), and 1920 μm (838~2814), respectively (Table 1). Of the 22 patients included, causative genes were identified in 15 patients (68.2%), and eight (36.4%) were EYS associated (Table 1). The patients underwent HFA testing and OCT imaging an average of 4.5 ± 0.92 times over 3.5 ± 0.90 years (shown as average ± SD). The MD and total point score derived by HFA showed a high correlation with EZ length at baseline (R = 0.87 and R = 0.86; P = 1.12E-07 and P = 2.78E-07, respectively) (Figs. 3A, 3B). The central ONL thickness was also correlated with MD values and total point score values on HFA (R = 0.68 and R = 0.71; P = 0.02 and P = 0.02, respectively) (Figs. 3E, 3F). The correlation between the central retinal thickness or central OS+ retinal thickness and the MD or the total point score was not statistically significant (Figs. 3C, 3D, 3G, 3F).

Disease Progression Detection, Change Speed, and Interinspection Fluctuations for the Different Measurements

On linear regression, the annual changes in the MD and total point score were −0.23 dB/yr (−0.34~−0.12) and −17.9 dB/yr (−26.2~−12.8), respectively. The annual changes in EZ length, central retinal thickness, central ONL thickness, and central OS+ thickness were −75.9 μm/yr (−96.9~−65.4), −1.1 μm/yr (−2.6~0.3),
Figure 2. Hypothetical ideal examinations. (A, B) Hypothetical ideal examinations that start from the value of 200 and progress constantly with an annual −5 (A) or −10 (B) decrease without fluctuation. The progression detection ability factor was calculated as 4.5E-07. (C, D) Hypothetical ideal examinations that start from the value of 2000 (C) or 2.0 (B) and progress constantly with an annual −100 (C) or −0.10 (D) decrease without fluctuation. The progression detection ability factor was calculated as 4.5E-07. (E, F) A hypothetical examination that starts from the value of 200 and progresses constantly with an annual −5 (E) or −10 (F) decrease and fluctuates by 5 from the ideal examinations without fluctuation. The progression detection ability factors were calculated as 1.0 (E) and 0.3 (F), respectively. (G, H) A hypothetical examination that starts from the value of 200 and progresses constantly with an annual −5 (G) or −10 (H) decrease and fluctuates by 20 from the ideal examinations without fluctuation. The progression detection ability factors were calculated as 16.0 (G) and 4.0 (H), respectively.

−1.9 μm/yr (−2.3~0.8), and −0.9 μm/yr (−2.8~0.7), respectively (Table 2). The percentage annual decrease rates were −1.9%/yr (−4.0~−0.9) in MD value, −1.3%/yr (−2.6~−0.9) in total point score, −4.8%/yr (−11.5~−2.4) in EZ length, −0.5%/yr (−1.5~0.1) in central retinal thickness, −0.2%/yr (−1.9~0.6) in central ONL thickness, and −1.2%/yr (−3.4~1.3) in central OS+ thickness, respectively (Table 2). RP progression was considered significant for an annual change of <0 and $P < 0.05$ for the linear regression (for
Table 1. Clinical Characteristics of the Subjects

| Characteristic                          | Patients With RP |
|----------------------------------------|------------------|
| Sex (male/female), n                    | 9/13             |
| Age (yr), median (Q₁∼Q₃)               | 48 (41∼57)       |
| MD value (dB), median (Q₁∼Q₃)          | −13.2 (−16.3∼−10.7) |
| Total point score (dB), median (Q₁∼Q₃) | 1323 (1150∼1529) |
| Visual acuity (logMAR), median (Q₁∼Q₃)| 0.07 (0.00∼0.15) |
| EZ length (μm), median (Q₁∼Q₃)         | 1920 (838∼2814)  |
| Central retinal thickness (μm), median (Q₁∼Q₃) | 251 (221∼273) |
| Central ONL thickness (μm), median (Q₁∼Q₃) | 121 (106∼149)   |
| Central OS+ thickness (μm), median (Q₁∼Q₃) | 74 (63∼83)      |

Causative gene, n (%)

- EYS: 8 (36.4)
- RP1L1: 2 (9.1)
- USH2A: 2 (9.1)
- RPGR: 1 (4.5)
- RHO: 1 (4.5)
- PDE6B: 1 (4.5)
- Unsolved: 7 (31.8)

Q₁, first quartile; Q₃, third quartile.

logMAR visual acuity, the progression was regarded as significant if the annual change was >0 and \( P < 0.05 \) for the linear regression, and significant disease progression was more frequently detected based on EZ length derived from OCT images (12/22 eyes) than based on the MD or total point score derived by HFA 10-2 (3/22 eyes; \( P = 0.004 \)), logMAR visual acuity (0/22 eyes; \( P < 0.0001 \)), central retinal thickness or central ONL thickness (1/11 eyes; \( P = 0.012 \)), and central OS+ thickness (2/11 eyes; \( P = 0.046 \), \( \chi^2 \) test) (Table 2).

Next, the values of the examinations with different units were compared using standardized values. The annual change was the fastest for EZ length (−0.67; −0.74∼−0.59), followed by the total point score (−0.38; −0.58∼−0.23) and MD (−0.32; −0.53∼−0.17) (Table 3). The least absolute values were lowest for EZ length (0.25; 0.19∼0.44), followed by central OS+ thickness (0.50; 0.24∼0.61) (Table 3).

Moreover, considering the possibility that the aforementioned comparisons may be different between eyes with or without central retinal thickness or epiretinal membrane, the annual change and the least absolute values using standardized values were separately compared between examinations of only eyes without macular edema or epiretinal membranes. Additionally, the annual change was found to be the fastest for EZ length followed by the total point score, whereas the least absolute values were also lowest for EZ length (Supplementary Table S1).

Progression Detection Ability Factor for the Actual Examination of the Subjects With RP

The progression detection ability factors of the subjects included in this study were 2.7 (0.8∼6.4) for MD, 2.3 (0.8∼4.5) for total point score, 8.6 (1.2∼19.0) for visual acuity, 1.2 (0.6∼7.0) for central retinal thickness, 1.4 (0.6∼2.1) for central ONL thickness, 0.8 (0.2∼2.9) for central OS+ thickness, and 0.2 (0.1∼0.5) for EZ length. The factor was lower in EZ length than in MD value or total point score (\( P = 0.025 \) and \( P = 0.006 \), respectively, paired \( t \)-test) (Table 4). The progression detection ability factor calculated only for eyes without macular edema or epiretinal membranes was also found to be the lowest for EZ length measurement (Supplementary Table S2).

A representative case of a 53-year-old man is presented in Figure 4. On linear regression, the annual changes in the MD, total point score, and EZ length were −0.11 dB/yr, −12.3 dB/yr, and −91.9 μm/yr, respectively. Of these, progression was only detected with EZ length (\( P = 0.68 \), \( P = 0.49 \), and \( P = 0.025 \), respectively, linear regression using the least-squares method).

Discussion

In the current study, we compared the functional and morphological findings widely used for monitor-
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Figure 3. Correlations between the visual field values and the values measured on OCT at baseline. (A) MD derived by the HFA 10-2 visual field test correlates with EZ length on OCT ($R = 0.87; P = 1.12E-07$). (B) Total point score derived by the HFA 10-2 visual field test was correlated with EZ length on OCT ($R = 0.86; P = 2.78E-07$). (C) MD derived by HFA 10-2 was not significantly correlated with central retinal thickness measurement on OCT ($R = 0.54; P = 0.08$). (D) Total point score derived by HFA 10-2 was not significantly correlated with central retinal thickness measurement on OCT ($R = 0.58; P = 0.06$). (E) MD derived by HFA 10-2 was correlated with central ONL thickness measurement on OCT ($R = 0.68; P = 0.02$). (F) Total point score derived by HFA 10-2 was correlated with ONL thickness measurement on OCT ($R = 0.71; P = 0.02$). (G) MD derived by HFA 10-2 was not significantly correlated with central OS+ thickness, measured as the distance between the EZ and choroid/Bruch’s membrane, on OCT ($R = 0.52; P = 0.10$). (H) Total point score derived by HFA 10-2 was not significantly correlated with central OS+ thickness on OCT ($R = 0.54; P = 0.09$).

The rate of detection of disease progression by linear regression analysis was evaluated. Second, the measurements were compared after standardization. Third, we devised a progression detection ability factor, which shows the magnitude of fluctuation, as well as the speed of the progression, and used it to compare the sensitivities of the examinations for detecting the progression of RP.
Table 2. Annual Change and Detection of Disease Progression on Linear Regression

| Measured Value                      | Annual Change (Percent Reduction) | Detection of Progression, n |
|-------------------------------------|-----------------------------------|-----------------------------|
| MD value (dB/yr)                    | 0.23 (−0.34~−0.12)                | 3/22                        |
| Total point score (dB/yr)           | −17.9 (−26.2~−12.8)               | 3/22                        |
| Visual acuity (logMAR/yr)           | −0.000 (−0.010~0.019)             | —                           |
| EZ length (μm/yr)                   | −75.9 (−96.9~−65.4)               | 12/22                       |
| Central retinal thickness (μm/yr)   | −1.1 (−2.6~−0.3)                  | 1/11                        |
| Central ONL thickness (μm/yr)       | −1.9 (−2.3~−0.8)                  | 1/11                        |
| Central OS+ thickness (μm/yr)       | −0.9 (−2.8~−0.7)                  | 2/11                        |

Table 3. Annual Change and Fit for Linear Regression of Standardized Measured Values

| Measured Value                      | Least Absolute Value | Annual Change |
|-------------------------------------|----------------------|---------------|
| MD value                            | 0.61 (0.43~0.66)     | −0.32 (−0.53~−0.17) |
| Total point score                   | 0.57 (0.47~0.63)     | −0.38 (−0.58~−0.23) |
| Visual acuity (logMAR)              | 0.64 (0.50~0.71)     | 0.01 (−0.20~0.44)  |
| EZ length                           | 0.25 (0.19~0.44)     | −0.67 (−0.74~−0.59) |
| Central retinal thickness (μm/yr)   | 0.56 (0.41~0.67)     | −0.31 (−0.61~0.20)  |
| Central ONL thickness               | 0.52 (0.42~0.62)     | −0.19 (−0.61~0.47)  |
| Central OS+ thickness               | 0.50 (0.24~0.61)     | −0.31 (−0.66~0.45)  |

Table 4. Comparison of Progression Detection Ability Factor Between Examinations

| Measured Value                      | Progression Detection Ability Factor, Median (Q₁~Q₃) |
|-------------------------------------|------------------------------------------------------|
| MD value                            | 2.7 (0.8~6.4)                                        |
| Total point score                   | 2.3 (0.8~4.5)                                        |
| Visual acuity (logMAR)              | 8.6 (1.2~19.0)                                       |
| EZ length                           | 0.2 (0.1~0.5)                                        |
| Central retinal thickness (μm/yr)   | 1.2 (0.6~7.0)                                        |
| Central ONL thickness               | 1.4 (0.6~2.1)                                        |
| Central OS+ thickness               | 0.8 (0.2~2.9)                                        |

*Progression detection ability factor = average of least squares/(annual change)^2.*

The disease course of RP is monitored both functionally and morphologically. In addition to visual acuity, automated perimetry is widely used for functional monitoring.22,23,26–28 Morphological factors that have been shown to correlate with functional measurements include EZ length and ONL or OS+ thickness.10,13,14,18

All three methods of comparison showed that EZ length derived from the OCT images was the most sensitive for detecting the progression of RP; it had a relatively higher change speed without smaller interinspection fluctuations than the others, including MD or total point score derived by HFA 10-2, visual acuity, and thickness of retinal layers.

The progression detection ability factor, devised in the current study, shows the magnitude of fluctuation, as well as the speed of the progression. The fluctuations between inspections disturb the detection of disease progression and hinder the assessment of disease progression and the effectiveness of therapies. Examinations with smaller fluctuations and faster progressions are more sensitive for detecting RP progression. The index can be used to evaluate the most suitable examination for detecting the progression of any disease. Because the index was calculated by dividing the average of the least squares by the squares of annual change, it could not be calculated for examinations with constant values.

New equipment has been developed within the past decades; the development of OCT and widefield fundus imaging systems has drastically changed ophthalmologic examinations.29,30 More recently, the development of adaptive optics–coordinated ophthalmic equipment has enabled the observation of fine structures such as photoreceptors,31–35 blood
Figure 4. A case of a 53-year-old woman with non-syndromic retinitis pigmentosa. The right eye was included in the study. (A) The annual change in the MD was calculated as $-0.11$ dB/yr based on linear regression using the least-squares method, although no statistically significant progression was detected ($P = 0.68$). (B) The annual change in the visible EZ length was calculated as $-91.9$ μm/yr, and it was statistically significant ($P = 0.025$). (C, left row) OCT images of the right eye; the visible ellipsoid zone length was measured on OCT images (white arrowheads). (Right row) HFA 10-2 visual field test (grayscale) results for the right eye.

flow, and retinal nerve fiber bundles. The progression detection ability factor will help us to assess new equipment appropriately.

The current study has several limitations. First, eyes with disease at relatively early and advanced stages were evaluated together. Different measurements may be suitable for different disease stages. Second, this study evaluated examinations performed annually. The irregularity of the examinations may influence the disease monitoring outcomes. Finally, retinal thickness was not assessed for cases with cystoid macular edema or epiretinal membrane; therefore, disease progression detection using retinal layer thickness for eyes with these conditions was not evaluated.
In conclusion, EZ length was more sensitive for detecting disease progression than visual field values, visual acuity, and retinal layer thickness. EZ length can be a sensitive outcome measure in future clinical trials.

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