

Title	Concentric division of 10 ° visual field tests in retinitis pigmentosa.
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## Introduction

Retinitis pigmentosa (RP) is a hereditary heterogeneous disease, which primarily affects rod photoreceptors. As a consequence of rod photoreceptor death, patients experience night blindness and peripheral visual field (VF) loss in the early stages of the disease.<sup>1</sup> Although cone photoreceptors are not the primarily affected cells in typical RP, devastating rod photoreceptor loss eventually leads to cone photoreceptor death. The loss of cone photoreceptors result in central VF loss and visual acuity (VA) impairment that has more critical influence in urbanized societies compared to night blindness or peripheral VF loss. Thus, it is important for RP patients to evaluate the remaining function of cone photoreceptors. Automated static perimetry such as Humphery Field Analyzer (Carl Zeiss Meditec, Inc. Dublin, CA) is one potential method for the purpose.<sup>2-7</sup> Several studies and large clinical trials,<sup>8-9</sup> use the measurement of HFA as a primary endpoint of the effect.

10-2 visual field testing program is a pre installed program of HFA that measures 68 points within central 10 degree. Because other programs use much less measuring pints in the central area (for example, 30-2 program lays only 12 points within 10 degree), 10-2 program might be better to evaluate the central

visual function and indeed, the advantage of 10-2 program in evaluating RP patients has been investigated **3**.

Sectorization of the VF has been proposed in glaucoma and succeeded in detecting changes in the threshold value.<sup>10-13</sup> Because RP patients shows concentric restriction of VF, we hypothesized that novel concentric sectorization of 10-2 program would be more useful to monitor the VF changes in RP patients. In this study, we retrospectively analyzed the mean sensitivity value in each concentrically divided sector of HFA 10-2 testing and investigated the efficacy of VF sectorization in evaluating the RP patients.

## Patients and Methods

We reviewed the clinical records of 415 patients who were diagnosed with RP at Kyoto University Hospital. The diagnosis of RP was made with night blindness, characteristic fundus appearance, concentric or ring-shaped scotoma and low amplitudes of electroretinogram in rods. We selected the patients who had constantly (five or more tests during 3.5 years or more) examined with the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Inc. Dublin, CA) 10-2 SITA standard program. The first data of HFA in each patient was not included in the analysis to overcome the learning effect. The data with fixation loss scores of 20% or more or false-positive or false-negative errors of 33% or more were also discarded.<sup>14</sup> The patients who received any intervention e.g. cataract surgery or medication of vitamin A during the follow up period were excluded. As a result, 37 eyes of 19 RP patients were included in the study. The VF of all 19 patients showed central constriction within 10 degree with or without peripheral islands of VF.

The mean deviation (MD) for central 10-2 visual field was calculated from total deviation with the Humphrey STATPAC. To achieve sector analysis,

the 68 measuring points of HFA 10-2 program were divided by six circular lines (Figure 1A). Then, the sectors were defined as six concentric sectors (Figure 1B, S1, S1-2, S1-3, S1-4, S1-5, S1-6) and six circular sectors (Figure 1C, S1, S2, S3, S4, S5, S6). In the study, sector analyses were performed based on the numerical value (NV) obtained from the result of each HFA field test. (Figure 1A) Each NV represents the sensitivity (dB) at each point and mean sensitivity of each sector was calculated by averaging the NVs included in each sector. The serial values of the mean sensitivity in each eye were analyzed with univariate linear regression and the time-dependent change of sensitivity was examined statistically by analysis of variance. To compare the sensitivity of detecting progression of VF between the MD and the NV of total 68 points, we used chi-square test.

Best-corrected visual acuity (VA) was measured with a Landolt chart and was converted to a logarithm of the minimum angle of resolution (logMAR). OCT images were obtained from all patients using Spectralis+OCT (Heidelberg Engineering, Heidelberg, Germany) at the end of the follow up period. We measured the length of the junction between inner segments and outer segments (IS/OS) manually in the 30 degree cross scans. Mann-Whitney U

test was performed to compare the lengths of IS/OS line of independent 2 groups. We performed all the statistical analysis in this study using PASW Statistics version 17.0 (SPSS, Chicago, IL)

## Results

The characteristics of the cases included in the study are summarized in Table 1.

The median age was 51 years (range 29-75, eight men and eleven women) at the beginning of follow-up. The median follow-up period was 4.5 years (range 3.5-8) and the median number of VF tests during the follow-up period was 6 (range 5-8).

### ***Mean Deviation VS Numerical Value in 68 points***

In the study period, the average rates of decline in the MD and the NV of whole points (S1-6) were  $-0.401 \pm 0.544$  dB/year ( $R^2 = 0.450 \pm 0.331$ ) and  $-0.486 \pm 0.583$  dB/year ( $R^2 = 0.429 \pm 0.327$ ), respectively. The linear regression showed that significant progression of VF was noted in 10 eyes in the MD and 11 eyes in the NV. The sensitivity in detecting the progression of VF was showed no difference between the MD and the NV ( $P = 1.000$ ).

### ***Concentric sectors analysis***

The  $R^2$  value represents how closely the data conform to a linear

relationship. To elucidate the proper size of VF tests in RP patients, this concentric sectors analysis was performed. Among the concentric sectors (S1, S1-2, S1-3, S1-4, S1-5, S1-6), fifteen eyes showed the best fit between the data and the regression line at S1 (Figure 2). Interestingly, the  $R^2$  values were low in the intermediate sectors S1-2, S1-3, S1-4, while seven eyes had the best fit in S1-5 and S1-6 (Figure 2). As the results of linear regression analysis of all eyes, the mean  $R^2$  and mean annual rate of decline about concentric sectors was shown in Table 2. Since Figure 2 showed bipolar distribution in both extremes, we divided them into 2 groups: best fitting to regression was seen in central area S1, S1-S2, S1-S3 and in larger area S1-S4, S1-S5, S1-S6. The eyes showing the best fitting to regression line within S3 area had significantly shorter IS/OS line (median, 454.5  $\mu\text{m}$ ) than did the other eyes (median, 825.5  $\mu\text{m}$ ). ( $P = 0.043$ ) The left eye of patient #10 represented the former eyes (Figure 4) and the right eye of patient #1 represented the latter eyes (Figure 5).

### ***Circular sectors analysis***

To illuminate the point in which the VF of RP patients is changing, we adopted the circular sectors analysis. S1 had the highest rate of decline in 15



eyes, while S6, peripheral region in the VF of 10 degree was the most progressive sector in 11 eyes (Figure 3). The mean R2 and mean annual rate of decline about circular sectors was shown in Table 3.

Since Figure 3 also showed bipolar distribution in both extremes, we divided them into 2 groups: best fitting to regression was seen in central area S1, S2, S3 and in larger area S4, S5, S6. The eyes showing the progression within S3 tended to have shorter IS/OS (median, 454.5  $\mu\text{m}$ ) than did the other eyes (median, 801.25  $\mu\text{m}$ ). (P = 0.100)

## Discussion

In the present study, we showed that an area of central VF, which is optimal to monitor the changes in RP patients, is different among each patient. Patients with severe VF constriction generally showed best fitting to regression and most significant progression in the most central area. Meanwhile, patients whose VF remains in 10 degree showed best fitting to regression and significant progression in the border of 10 degree field.

RP is a hereditary retinal disease and the major cause of visual handicap or blindness also in Japan. Although taking vitamin A showed slower decline in electroretinogram, there has been no treatment to improve or preserve the visual function of the patients.<sup>15</sup> One reason for the difficulty in developing novel treatments is the absence of practical evaluation system for disease progression; visual acuity does not change for a long time, electroretinogram has inter-examination variation, and kinetic perimetry is not suitable for quantitative analysis. Some recent large clinical trials adopted the change of VF threshold measured with HFA 30-2 program as the main outcome but they could not show sufficiently the effect of the treatment.<sup>8-9</sup> In order to detect the probably small response to such treatment, it is essential to establish another strategy for the

estimation of VF that has a higher sensitivity.

RP typically shows ring-shaped scotoma, which advances to remains only central visual field within 10 degree. Thus, some researchers investigated and reported the usefulness of HFA 10-2 program.<sup>7</sup> In fact, Nakazawa et al. recently showed that taking nilvadipine retarded progression of HFA 10-2 scores in a small study.<sup>16</sup> It has not been, however, elucidated whether measurement of the 10 degree VF is most suitable to follow the visual field of patients with RP. After Hirakawa et al. reported the 10-2 FASTPAC program about RP, SITA program was developed to reduce the examination time.<sup>17</sup> We observed the central visual field of RP patients with HFA 10-2 SITA standard program at Kyoto University Hospital since 2003 and assessed the concentric sectorial analysis within 10 degree in this retrospective study.

The MD of HFA is calculated using total deviation with Humphrey STATPAC. The total deviation is estimated by subtracting the median value of healthy people from the NV. We hypothesized that MD, which would be a better parameter to distinguish patients from healthy people, might have lower power to detect the change of longitudinal data. Actually, the clinical trials of docosahexaenoic acid or Lutein in patients with RP used the total point score of

NV of HFA. Unexpectedly, however, our result did not reveal the statistical difference between MD and mean NV of total 68 points (S1-6) in detecting the progression. .

Considering that increase of measurement points mathematically makes the variance smaller, the mean sensitivity of total 68 points (S1-6) should have been better to fit the regression line than the mean of central 4 points (S1). Surprisingly, however, our result demonstrated that 41% of all the eyes had the best score of  $R^2$  at the central sector (S1). Furthermore, S1 had also the highest rate of decline in 41%. The result shows that the measurement values are not a simple stochastic event. The threshold in central visual field would have less variability compared to peripheral one. The result suggests that monitoring the changes of S1 sector would make it easier to detect the change of VF in patients with RP than monitoring total VF of 10 degree.

Rangaswamy et al. investigated the relationship between HFA and IS/OS and showed that the termination of the IS/OS border corresponded to VF loss of -10 dB.<sup>18</sup> To evaluate the relationship between HFA and retinal morphology, we also measured the length of IS/OS and compared them between cases with highest correlation coefficient in inner sectors and in outer

sectors. The analysis showed that those with highest correlation coefficient in inner sectors have shorter IS/OS; in other words, those with shorter IS/OS tended to show reproducible and significant decline of VF in inner sectors. The result indicates that we should monitor different part of VF depending on the remaining retinal morphology or function.

There were several limitations to the present study, retrospective design, one institution based sample size, possible selection bias in that they underwent HFA for a long period. Especially, included eyes in this study had small VF limited within 10 degree with/without far peripheral VF islands. Some younger patients with RP have larger VF than 10 degree in their central vision. If they were include in this study, the distribution of the best fitting sector or the most progressive sector would be shifted to more peripheral sectors and the proper program would be 30-2 program rather than 10-2. But, at least, in the eyes with concentric VF loss within 10 degree, it would be safe to say that the mean sensitivity of central 4 points (S1) in 10-2 program is a good parameter to follow up and detect the decline of sensitivity. We need further studies to optimize the VF tests for the purpose of effective follow-up of the patients with RP and designing clinical trials to test the efficacy of any treatments.

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## Figure legends

Figure 1. The sectorization of 10 degree visual field test

concentric sectorization of numerical value and grey scale (a), unified sectors for the analysis of goodness of fitting (b), single sectors for the analysis of the annual rates of decline (c), S1 was composed of central 4 points, S2 was 8 points around S1, S3 was 12 points around S2, S4 was 16 points around S3, S5 was 20 points around S4, and S6 was 4 points

Figure 2. The distribution of the best fitting sectors in the concentric sector analysis

The number of eyes which had the best score of  $R^2$  at each concentric sector is shown in the bar graph.

Figure 3. The distribution in the circular sector analysis

The number of eyes which had the highest rate of decline (a) and the best score of  $R^2$  (b) at each circular sector are shown in the bar graph.

Figure 4. Color fundus photograph (a), the horizontal scan of optical coherence tomography (b), the vertical scan (c), the grey scale (d), the linear regression of unified sectors (e) and the linear regression of each sector (f) in the left eye of patients #10

Figure 5. Color fundus photograph (a), the horizontal scan of optical coherence tomography (b), the vertical scan (c), the grey scale (d), the linear regression of unified sectors (e) and the linear regression of each sector (f) in the right eye of patients #1

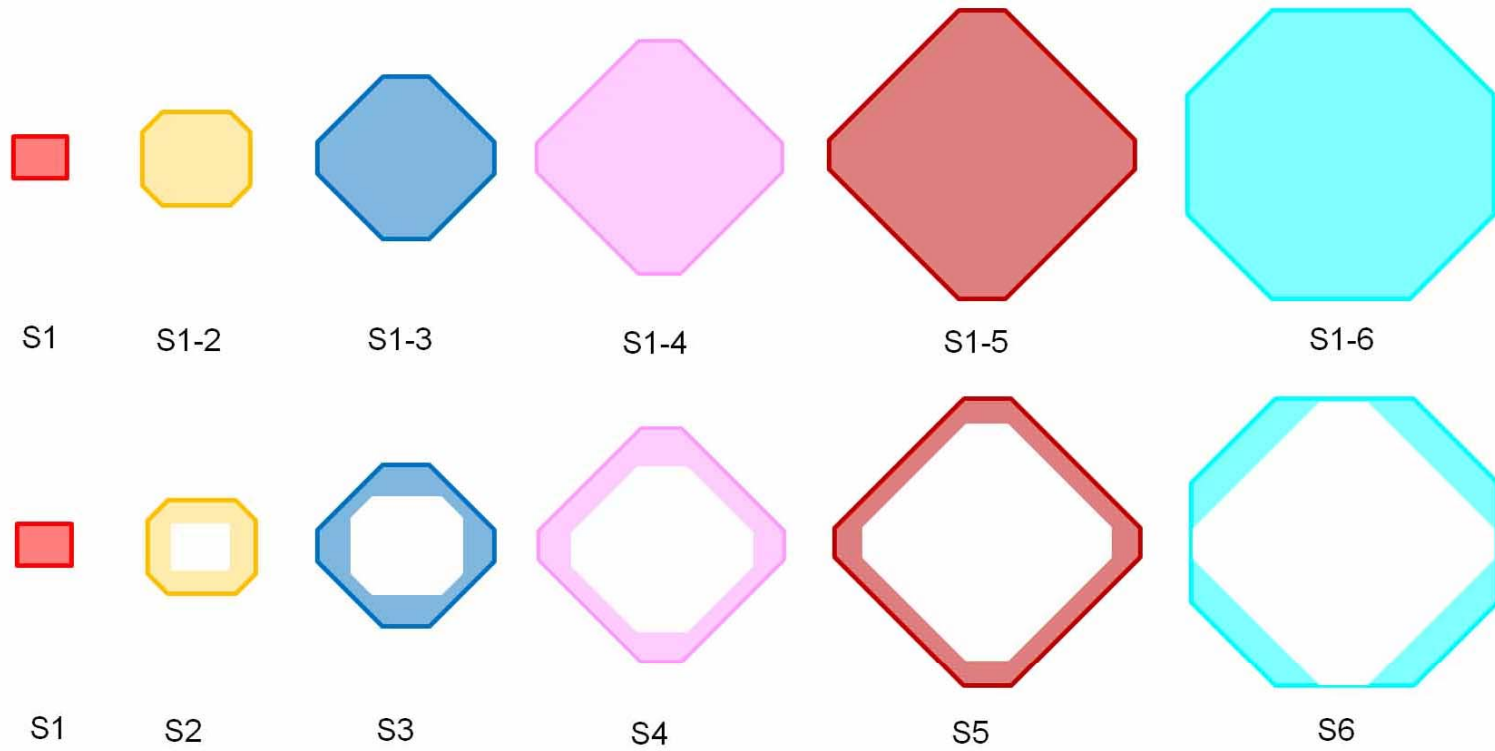
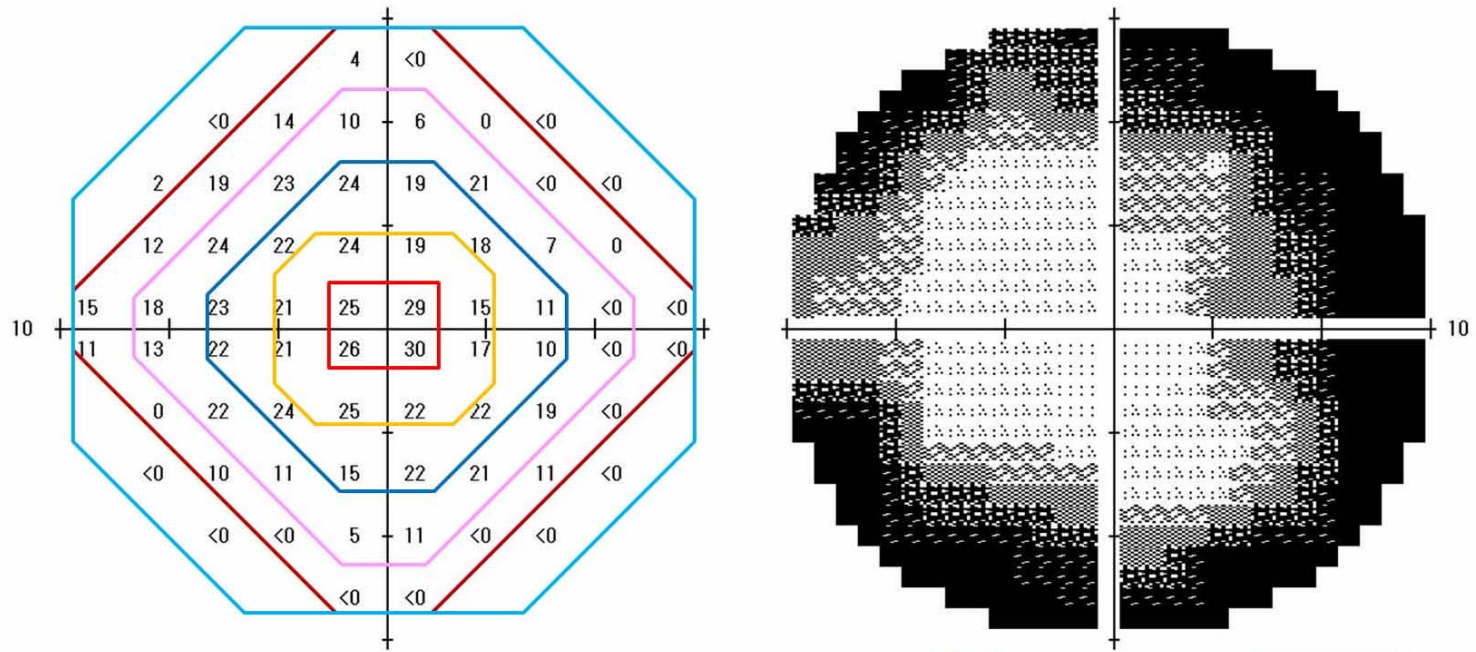


Figure 1

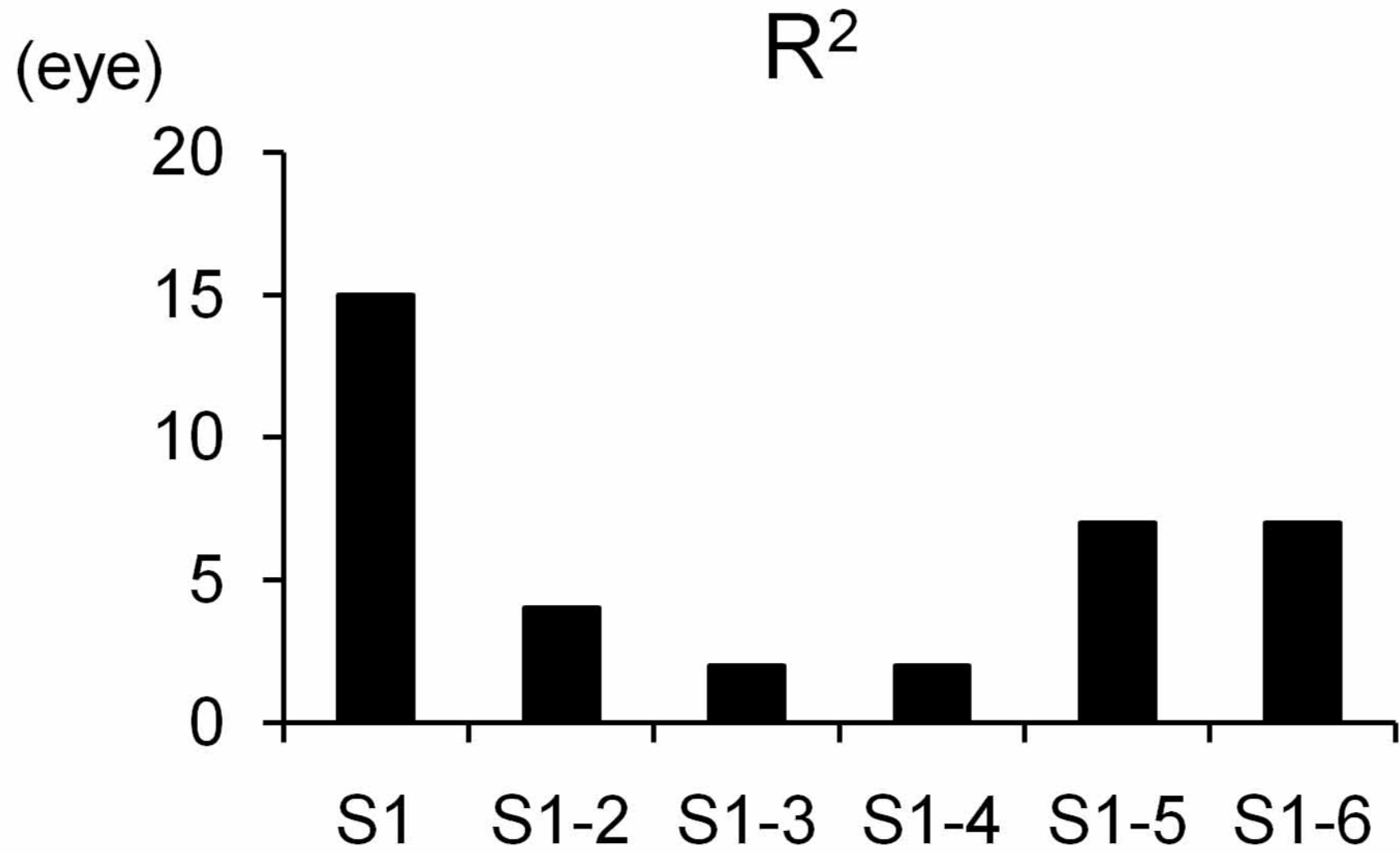


Figure 2

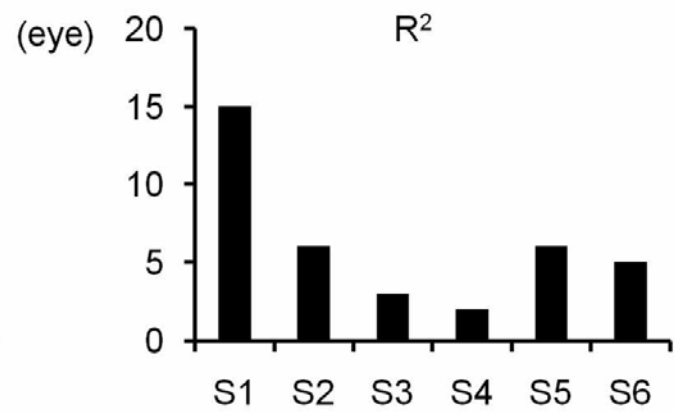
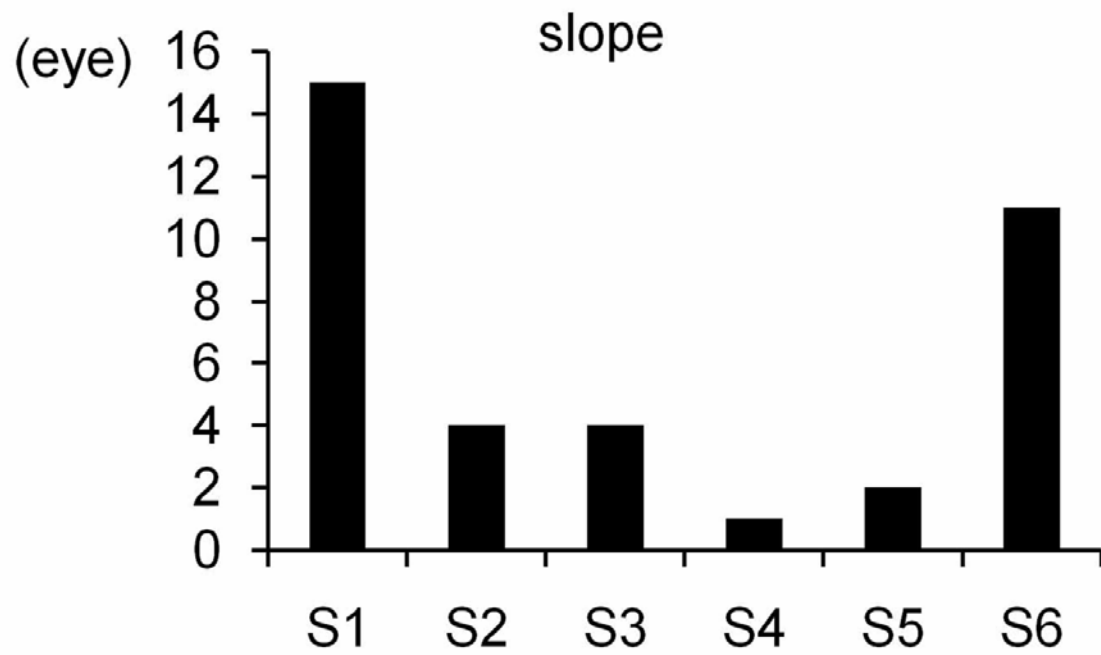


Figure 3

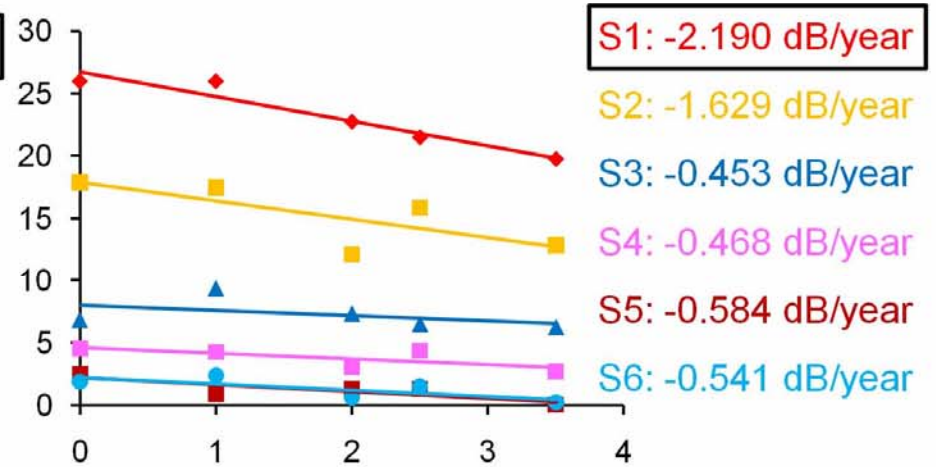
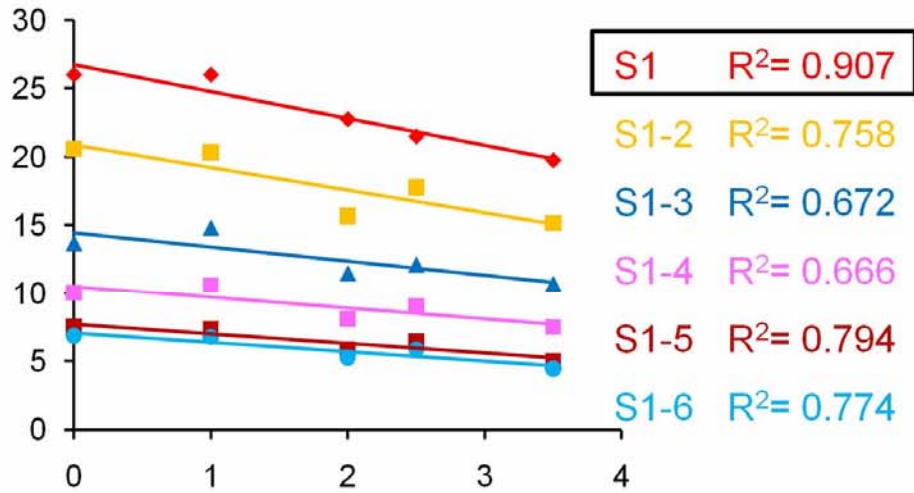
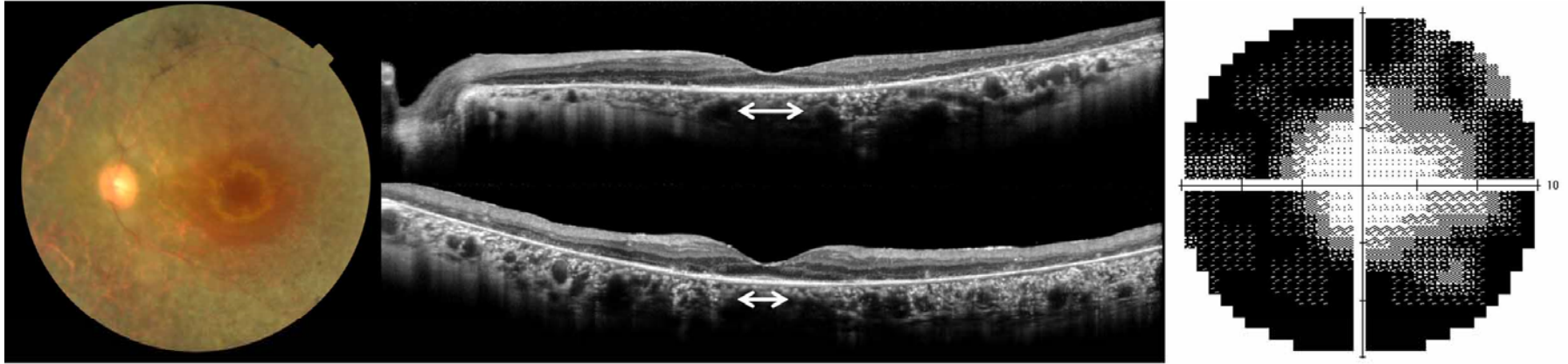


Figure 4

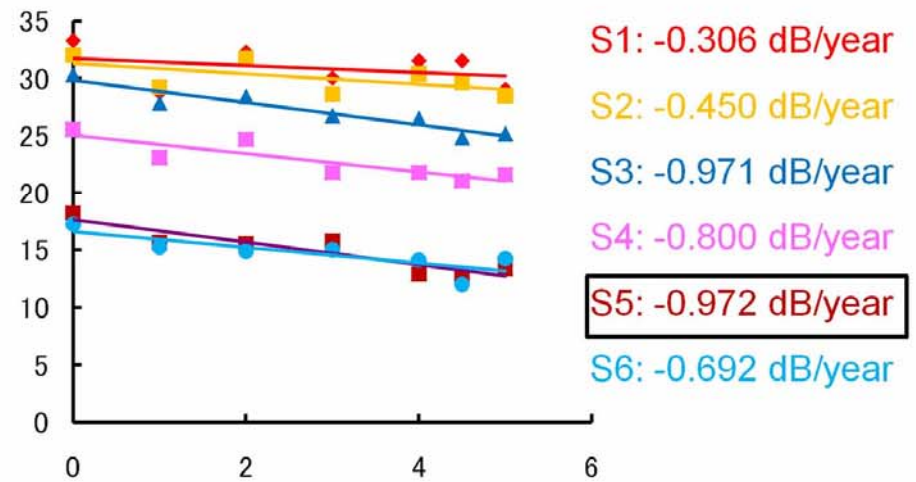
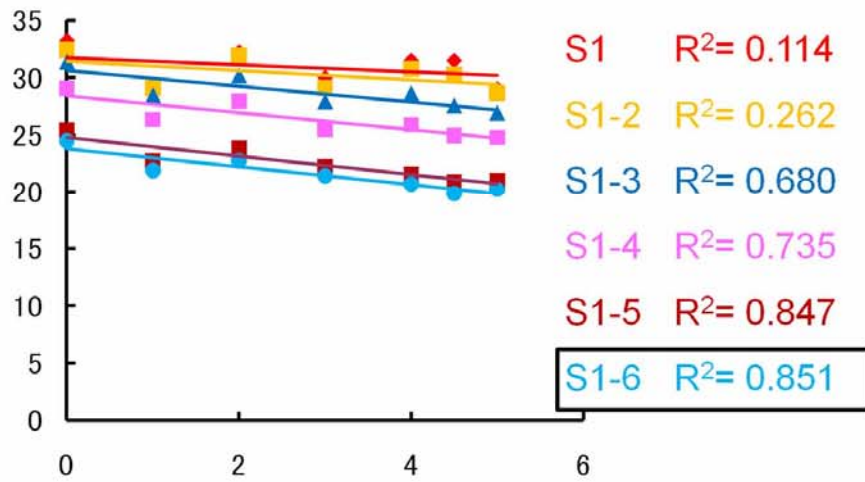
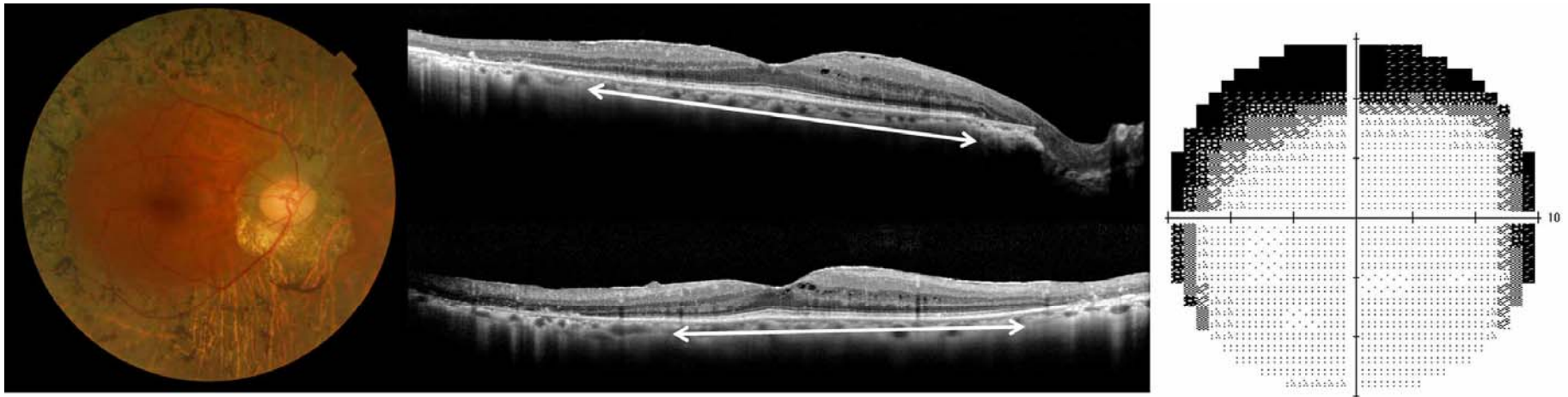


Figure 5

Table 1 Characteristics of patients

Patient number, initial age, gender	Inheritance pattern	eye	Follow-up period (year)	Number of field tests	Visual Acuity (logMAR)		Mean Deviation (dB)	
					initial	final	initial	final
1, 73, M	Sporadic	L	5.5	6	-0.08	0.00	-4.6	-6.69
		R	5.5	7	0.05	0.00	-9.2	-10.75
2, 48, M	Sporadic	L	7	8	-0.08	0.00	-15.8	-16.98
		R	7	8	0.00	-0.18	-14.71	-14.87
3, 44, M	Sporadic	L	4.5	6	0.82	1.00	-17.15	-17.68
		R	4.5	6	0.40	0.52	-17.38	-19.44
4, 54, M	AR	L	3.5	5	0.00	0.00	-19.19	-20.86
		R	3.5	5	0.22	0.10	-17.89	-19.49
5, 48, M	AD	L	4.5	5	0.15	0.52	-15.75	-19.42
		R	4.5	5	0.15	0.52	-16.01	-21.93
6, 34, F	AD	L	3.5	5	0.22	0.52	-27.45	-29.54
		R	3.5	5	0.22	0.40	-23.56	-26.54
7, 56, F	AD	L	4	6	0.00	0.00	-26.52	-27.63
		R	7.5	8	0.22	0.52	-23.31	-27.15
8, 75, F	AD	L	7.5	8	0.30	0.40	-28.21	-29.36
		R	5.5	5	0.70	1.40	-28.22	-31.21
9, 66, F	AD	R	4.5	5	0.52	1.52	-29.73	-30.09
10, 44, F	AD	L	3.5	5	0.10	0.22	-27.51	-29.93



		R	3.5	5	0.40	0.52	-34.95	-30.11
11, 56, F	AD	L	6.5	6	0.22	0.30	-29.65	-32.18
		R	6.5	6	0.22	0.52	-29.57	-32.24
12, 58, M	AD	L	3.5	6	0.15	0.15	-31.94	-32.27
		R	3.5	6	0.15	0.15	-31.93	-31.65
13, 29, F	Sporadic	L	5.5	6	-0.08	-0.08	-35.46	-35.19
		R	5.5	6	-0.08	-0.18	-35.73	-34.75
14, 57, M	Sporadic	L	6	6	0.30	0.30	-17.62	-16.86
		R	6	6	0.30	0.22	-11.98	-12.72
15, 41, F	AD	L	4	8	-0.18	-0.18	-0.95	-1.43
		R	4	8	-0.08	-0.18	-1.43	-0.95
16, 48, M	AD	L	3.5	6	0.05	0.15	-21.04	-23.68
		R	3.5	5	0.05	0.15	-22.39	-23.77
17, 58, F	Sporadic	L	4	5	0.05	0.00	-25.3	-25.94
		R	4	5	0.15	0.15	-23.93	-25.53
18, 46, F	AD	L	3.5	5	0.52	1.40	-22.56	-28.2
		R	3.5	5	0.30	0.52	-17.37	-25.93
19, 51, F	AR	L	8	7	0.70	1.00	-20.62	-24.64
		R	8	7	0.30	0.70	-19.72	-23.15
The annual rate of decline (mean $\pm$ standard deviation )					0.0412 $\pm$ 0.0642 (logMAR/year)		-0.401 $\pm$ 0.544 db/year	
The number of eyes showing significant progression					10		10	

Table 2 The annual rate of decline and R2 in the concentric sectors analysis

	<b>Slope (dB/year)</b>	<b>R2</b>
<b>S1</b>	$-0.511 \pm 1.267$	$0.437 \pm 0.309$
<b>S1-2</b>	$-0.504 \pm 0.849$	$0.418 \pm 0.308$
<b>S1-3</b>	$-0.500 \pm 0.708$	$0.413 \pm 0.320$
<b>S1-4</b>	$-0.502 \pm 0.627$	$0.417 \pm 0.322$
<b>S1-5</b>	$-0.448 \pm 0.577$	$0.432 \pm 0.333$
<b>S1-6</b>	$-0.486 \pm 0.583$	$0.429 \pm 0.327$

Table 3 The annual rate of decline and R2 in the circular sectors analysis

	<b>Slope (dB/year)</b>	<b>R2</b>
<b>S1</b>	$-0.511 \pm 1.267$	$0.437 \pm 0.309$
<b>S2</b>	$-0.505 \pm 0.742$	$0.357 \pm 0.309$
<b>S3</b>	$-0.497 \pm 0.708$	$0.334 \pm 0.314$
<b>S4</b>	$-0.461 \pm 0.661$	$0.370 \pm 0.320$
<b>S5</b>	$-0.442 \pm 0.627$	$0.407 \pm 0.305$
<b>S6</b>	$-0.488 \pm 0.651$	$0.409 \pm 0.320$