

# Detecting Progression of Retinitis Pigmentosa Using the Binomial Pointwise Linear Regression Method

Shotaro Asano<sup>1,2</sup>, Akio Oishi<sup>3,4</sup>, Ryo Asaoka<sup>1,5-8</sup>, Yuri Fujino<sup>1,5,9</sup>, Hiroshi Murata<sup>1</sup>, Keiko Azuma<sup>1</sup>, Manabu Miyata<sup>3</sup>, Ryo Obata<sup>1</sup>, and Tatsuya Inoue<sup>1,10</sup>

<sup>1</sup> Department of Ophthalmology, The University of Tokyo, Graduate School of Medicine, Tokyo, Japan

<sup>2</sup> Department of Ophthalmology, Asahi General Hospital, Asahi, Chiba, Japan

<sup>3</sup> Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

<sup>4</sup> Department of Ophthalmology and Visual Sciences, Nagasaki University, Nagasaki, Japan

<sup>5</sup> Department of Ophthalmology, Seirei Hamamatsu General Hospital, Shizuoka, Japan

<sup>6</sup> Seirei Christopher University, Shizuoka, Japan

<sup>7</sup> Nanovision Research Division, Research Institute of Electronics, Shizuoka University, Shizuoka, Japan

<sup>8</sup> The Graduate School for the Creation of New Photonics Industries, Shizuoka, Japan

<sup>9</sup> Department of Ophthalmology, Shimane University Faculty of Medicine, Izumo, Japan

<sup>10</sup> Department of Ophthalmology and Micro-Technology, Yokohama City University, Kanagawa, Japan

**Correspondence:** Ryo Asaoka, Department of Ophthalmology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo 113-8655, Japan. e-mail: [rasaoka-ky@umin.ac.jp](mailto:rasaoka-ky@umin.ac.jp)

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**Purpose:** A method of evaluating central visual field (VF) progression in eyes with retinitis pigmentosa (RP) has still to be established. We previously reported the potential merit of applying a binomial test to pointwise linear regression (binomial PLR) in glaucoma progression. In the current study, we investigated the usefulness of binomial PLR in eyes with RP.

**Methods:** A series of 10 VFs (VF 1–10, Humphrey field analyzer, 10-2 test) from 196 eyes of 103 patients with RP were collected retrospectively. The PLR was performed by regressing the total deviation of all test points with the complete series of 10 VFs. The accuracy (positive predictive value, negative predictive value, and false-positive rate) and the time required to detect VF progression with shorter VF series (from VF 1–5 to VF 1–9) were compared across the binomial PLR, a permutation analysis of PLR (PoPLR), and a mean deviation (MD) trend analysis.

**Results:** In evaluating VF progression, the binomial PLR was comparable with the PoPLR and MD trend analyses in its positive predictive value (0.55 to 0.95), negative predictive value (0.67 to 0.92), and false-positive rate (0.01 to 0.05). The binomial PLR required significantly less time to detect VF progression ( $5.0 \pm 2.0$  years) than the PoPLR and MD trend analyses ( $P < 0.01$ ,  $P < 0.001$ , respectively).

**Conclusions:** The application of a binomial PLR achieved reliable and earlier detection of central VF progression in eyes with RP.

**Translational Relevance:** A binomial PLR was useful in assessing VF progression in RP.

## Introduction

Retinitis pigmentosa (RP) is a progressive hereditary retinal disease caused by the degeneration of rod and cone photoreceptors.<sup>1,2</sup> RP is characterized by night blindness, loss of fine acuity, and a constricted visual field (VF).<sup>1</sup> VF can be measured with a Humphrey field analyzer (HFA) (Carl Zeiss Meditec,

Dublin, CA) in eyes with RP,<sup>3,4</sup> which typically have scotomas that enlarge over a period of years owing to the loss of rod and cone function.<sup>1</sup> Visual acuity can remain good even in advanced cases, typically with a small island of remaining central VF.<sup>1</sup> An assessment of central VF, such as the HFA 10-2 test, is of critical importance in evaluating visual disability.<sup>1,5</sup> However, a method of evaluating central VF progression in eyes with RP remains to be established.

The VF progression rate is usually evaluated by trend analysis. The mean deviation (MD) trend analysis is frequently used to clinically assess the rate of VF progression, with a HFA. However, it is not an ideal method to detect focal VF progression, because the MD is the average of VF damage over the entire VF. In contrast, an analysis can be undertaken using point-wise linear regression (PLR).<sup>6,7</sup> Previous studies have reported the advantage of PLR in the early detection of VF progression, particularly in glaucomatous eyes.<sup>8-12</sup> However, one drawback of PLR is that the progression over the entire VF cannot be analyzed.<sup>13</sup> The application of permutation analyses of PLR (PoPLR)<sup>14</sup> and binomial tests to PLR (binomial PLR)<sup>13,15,16</sup> are solutions to this problem. These methods integrate information on the VF progression rate at each test location, and enable an assessment to be made of VF progression as a whole. We previously reported that the binomial PLR yielded more reliable and earlier detection of VF progression than the MD trend analysis and PoPLR in cases of glaucomatous eyes.<sup>13,15,16</sup> Specifically, Karakawa et al.<sup>13</sup> reported that the binomial PLR method gives more consistent results than MD trend analysis or PoPLR in analyzing HFA 24-2 test results.

There is no treatment for RP, except retinal prosthesis for advanced cases<sup>17</sup> and gene therapy for patients with specific mutations.<sup>18</sup> The inability to evaluate the progression is one of the reasons why clinical trials have not been successful in RP. The establishment of sensitive and reproducible methods of evaluating VF progression is desirable. One example of this effort is a model to predict the central VF sensitivity from the structural damage demonstrated by fundus autofluorescence imaging in RP.<sup>19</sup> In the current study, we investigated whether binomial PLR is useful in evaluating VF progression in the central 10°, in eyes with RP.

## Methods

The study was approved by the Institutional Review Boards of the University of Tokyo and Kyoto University and adheres to the tenets of the Declaration of Helsinki. The study protocols did not require that each patient provide written informed consent. Instead, the protocol was posted at the outpatient clinic to notify participants of the study.

## Subjects

VF data were retrospectively obtained of 196 eyes in 103 patients with RP. Patients were followed in the retinal dystrophy clinics at the University of Tokyo

Hospital and Kyoto University Hospital between February 1, 2005, and January 31, 2020. All patients underwent at least 10 measurements with the 10-2 HFA test pattern, excluding the initial VF. Inclusion criteria in this study were (1) typical fundus findings of RP, such as bone spicule pigmentation, arteriolar attenuation, and waxy disc pallor; (2) a decrease in a-wave and b-wave amplitudes or nondetectable full-field electroretinogram; (3) RP was the only disease causing VF damage; (4) no other diseases of the anterior and posterior segments of the eye that could affect VF, including cataracts, except for clinically insignificant senile cataracts; and (5) patient age at least 20 years. Patients who underwent intraocular surgery, including cataract surgery, during the observation period were excluded. VF measurements were performed using HFA with the 10-2 program and the Swedish Interactive Threshold Algorithm standard. Reliability criteria for VFs were applied, including fixation losses of less than 20% and false-positive responses of less than 15%, following the manufacturer's recommendation. The VF of the left eye was mirror-imaged to that of the right eye for statistical analyses.

## MD Trend Analysis

In the MD trend analysis, the MD value was linearly regressed against time, using 10 VFs (VF<sub>1-10</sub>; the series of VFs from 1 to 10). We defined a series of VF tests to be significant if the MD slope was less than zero and the calculated *P* value was less than 0.025. Otherwise, it was not significant. In the current study, the progression assessment for VF<sub>1-10</sub> was regarded as a surrogate for the absolute true progression. Similar analyses were carried out with shorter VF sequences (from VF<sub>1-9</sub> to VF<sub>1-5</sub>), and their reliability (consistency) was evaluated through three surrogate measures for the true positive rate (the proportion of both VF<sub>1-10</sub> and shorter series progressing [PBP]); the true negative rate (the proportion of both VF<sub>1-10</sub> and shorter series not progressing [PBNP]); and the false positive rate (the proportion of inconsistent progression [PIP]). [Figure 1](#) shows the concept of PBP, PBNP, and PIP.

- (1) PBP is the probability that both the complete series of VFs (VF<sub>1-10</sub>) and each of the shorter series of VFs (from VF<sub>1-5</sub> to VF<sub>1-9</sub>) were classified as progressive.
- (2) PBNP is the probability that the complete series of VFs (VF<sub>1-10</sub>) and each of the shorter series of VFs (from VF<sub>1-5</sub> to VF<sub>1-9</sub>) were classified as not progressive.
- (3) PIP is the probability that each of the shorter series of VFs (from VF<sub>1-5</sub> to VF<sub>1-9</sub>) was classified

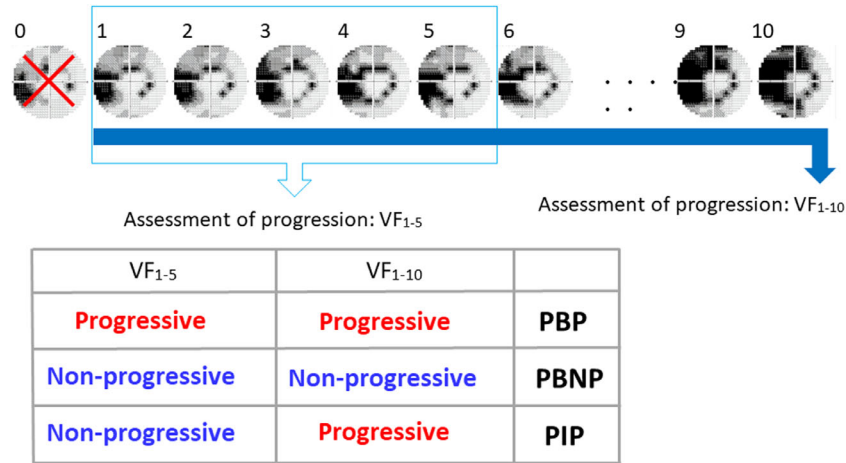


Figure 1. The demonstrative figure of PBP, PBNP, and PIP.

as progressive while the complete series of VFs (VF<sub>1-10</sub>) was classified as not progressive.

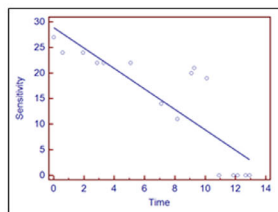
We also carried out a Kaplan–Meier survival analysis to compare the time required to detect progression, following our previous studies.<sup>13,16,20</sup>

- (4) The time required to detect progression was assessed using the Kaplan–Meier survival analysis, and compared using a log rank test.

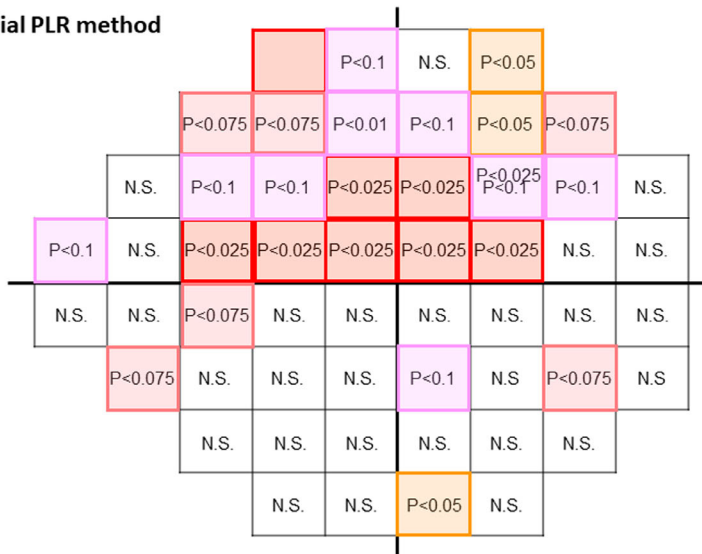
### Binomial PLR

The calculation of the binomial PLR method is described in detail in our previous reports.<sup>13</sup> The assumption in PLR is that VF damage progresses linearly over time. PLR analyses are usually conducted by regressing the total deviation values (as an independent variable) over time (as a dependent variable), similar to the MD and VFI trend analysis in the Guided Progression Analysis in HFA. Here, the null hypothesis

#### The calculation of the binomial PLR method



Calculation of P-value with linear regression at each test point



P-value with linear regression	Number of test points	P-value with binomial test
p<0.025	8	$5.3 \times 10^{-6}$
p<0.05	11	$7.7 \times 10^{-6}$
p<0.075	17	$2.0 \times 10^{-8}$
p<0.1	26	$3.8 \times 10^{-14}$

Median =  $2.7 \times 10^{-6}$

Figure 2. An example of calculating a P value with the binomial PLR method.

**Table.** Demographics of the Eyes

Variables	No. or Mean ± Standard Deviation
No. of eyes	196
No. of subjects	103
Eye laterality (right/left)	100/96
Age, years	47.7 ± 12.1
MD at the baseline, dB	-16.4 ± 8.0
Follow-up, years	8.1 ± 1.9
MD progression rate, dB/y	-0.55 ± 0.53

was that the change of the entire VF was equal to zero. Under this null hypothesis, the slope coefficient  $P$  value from linear regression at each test point is uniformly distributed between zero and 1. If we are to accept the null hypothesis, we would expect the numbers of test points to follow a binomial distribution. Hence, the numbers of test points with  $P$  values lower than 0.025, 0.050, 0.075, and 0.100 should follow the binomial distribution. If the null hypothesis is rejected, a slope coefficient of zero would be considered unlikely to be the result of random chance. Thus, the significance of the entire VF progression was assessed using these four cut-off  $P$  values. The median value was then used to determine progression to merge the four  $P$  values.<sup>21,22</sup> We defined a series of VF tests to be significant if the slope was less than zero and the  $P$  value calculated by binomial PLR was less than 0.025. Otherwise it was not significant. Figure 2 shows an example of calculating a  $P$  value with the binomial PLR method. Thereafter we calculated PBP, PBNP, PIP, and the Kaplan–Meier survival analysis with the log rank test, in a similar manner to the MD trend analysis.

### PoPLR

PoPLR uses the permutation analyses of PLR to sum the statistical significance for VF deterioration, according to the individual patient’s data (and its variability).<sup>14</sup> The PoPLR method was carried out with total deviation values at each test point, using the  $R$  package “visualFields” modified to deal with the HFA 10-2 test. Here, we defined a series of VF tests to be significant if the slope was less than zero and the  $P$  value calculated by PoPLR was less than 0.025. Otherwise it was not significant. We then calculated the PBP, PBNP, PIP, and the time required to detect a significant progression.

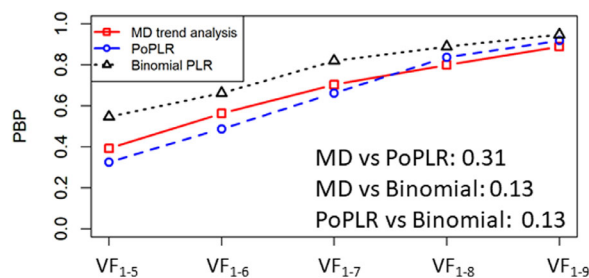
All statistical analyses were carried out using the statistical program  $R$  software (version 3.6.3; <http://www.r-project.org/>). The  $P$  values in multiple comparisons were corrected using the Hochberg correction.

## Results

Demographics of the eyes are shown in the Table. The average baseline MD was  $-16.4 \pm 8.0$  dB, and the initial age of the patients was  $47.7 \pm 12.1$  years. The mean observation period between VF<sub>1</sub> and VF<sub>10</sub> was  $8.1 \pm 1.9$  years. The average rate of MD progression was  $-0.55 \pm 0.53$  dB/y.

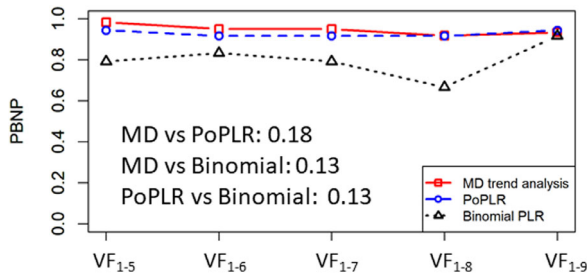
Figure 3 shows the PBP with the binomial PLR, PoPLR, and MD trend analysis. These values varied between 0.55 (VF<sub>1-5</sub>) and 0.95 (VF<sub>1-9</sub>) with binomial PLR, between 0.33 (VF<sub>1-5</sub>) and 0.92 (VF<sub>1-9</sub>) with PoPLR, and between 0.39 (VF<sub>1-5</sub>) and 0.89 (VF<sub>1-9</sub>) with MD trend analysis. There was no significant difference among the PBP values obtained with the three methods (all  $P$  values > 0.05, in a Wilcoxon signed rank test adjusted for multiple comparisons using the Hochberg correction).

Figure 4 shows the PBNP with binomial PLR, PoPLR, and MD trend analysis. These values varied between 0.67 (VF<sub>1-8</sub>) and 0.92 (VF<sub>1-9</sub>) with binomial PLR, between 0.92 (VF<sub>1-6</sub>, VF<sub>1-7</sub>, and VF<sub>1-8</sub>) and 0.94 (VF<sub>1-5</sub> and VF<sub>1-9</sub>) with PoPLR, and between 0.92 (VF<sub>1-8</sub>) and 0.98 (VF<sub>1-5</sub>) with MD trend analysis. There was no significant difference among the PBNP

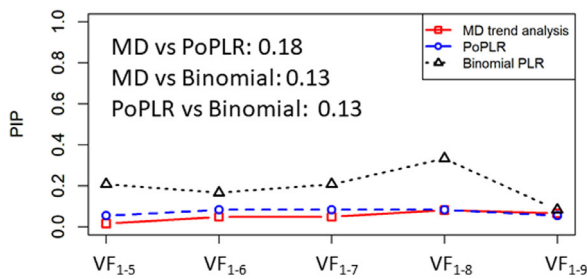


**Figure 3.** The rates of PBP with binomial PLR, PoPLR, and MD trend analysis. The rates of PBP were compared across binomial PLR, PoPLR, and MD trend analysis. There was no significant difference between the PBP rates of the four methods (all  $P$  values > 0.05, in a Wilcoxon signed rank test adjusted for multiple comparisons using the Hochberg correction).





**Figure 4.** The rates of PBNP with binomial PLR, PoPLR, and MD trend analysis. The rates of PBNP were compared across binomial PLR, PoPLR, and MD trend analysis. There was no significant difference between the PBNP rates of the four methods (all  $P$  values  $> 0.05$ , in a Wilcoxon signed rank test adjusted for multiple comparisons using the Hochberg correction).

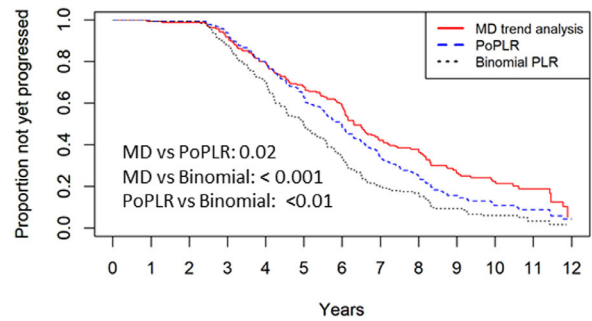


**Figure 5.** The rates of PIP with binomial PLR, PoPLR, and MD trend analysis. The rates of PIP were compared across binomial PLR, PoPLR, and MD trend analyses. There was no significant difference between the PIP rates of the four methods (all  $P$  values  $> 0.05$ , in a Wilcoxon signed rank test adjusted for multiple comparisons using the Hochberg correction).

values obtained with the three methods (all  $P$  values  $> 0.05$ , in a Wilcoxon signed rank test adjusted for multiple comparisons using the Hochberg correction).

**Figure 5** shows the PIP for binomial PLR, PoPLR, and MD trend analysis. These values ranged from 0.08 (VF<sub>1-9</sub>) to 0.33 (VF<sub>1-8</sub>) with binomial PLR, from 0.06 (VF<sub>1-5</sub> and VF<sub>1-9</sub>) to 0.08 (VF<sub>1-6</sub>, VF<sub>1-7</sub>, and VF<sub>1-8</sub>) with PoPLR, and from 0.02 (VF<sub>1-5</sub>) to 0.08 (VF<sub>1-8</sub>) with MD trend analysis. There was no significant difference among the PIP values obtained with the three methods (all  $P$  values  $> 0.05$ , in a Wilcoxon signed rank test adjusted for multiple comparisons using the Hochberg correction).

**Figure 6** shows the results of Kaplan–Meier survival analyses. Log rank test results indicate that the binomial PLR method detected progressions significantly earlier than PoPLR and MD trend analysis ( $P < 0.01$  and  $P < 0.001$ , respectively; log rank tests were adjusted for multiple comparisons using the Hochberg correction). PoPLR detected progression earlier than MD trend analysis ( $P = 0.02$ ; log rank tests were adjusted for multiple comparisons using the Hochberg correction). The mean times required



**Figure 6.** The Kaplan–Meier survival analysis with binomial PLR, PoPLR, and MD trend analysis. The results of the Kaplan–Meier survival analysis with binomial PLR, PoPLR, and MD trend analyses are shown. Log rank tests indicate that the binomial PLR method detected progression significantly earlier than PoPLR and MD trend analysis ( $P < 0.01$  and  $P < 0.001$ , respectively; log rank tests adjusted for multiple comparisons using the Hochberg correction). PoPLR detected progression significantly earlier than MD trend analyses ( $p = 0.02$ , log rank tests adjusted for multiple comparisons using the Hochberg correction).

to reach a diagnosis of progression with each method were as follows:  $5.0 \pm 2.0$  years with binomial PLR;  $5.5 \pm 1.9$  years with PoPLR; and  $5.4 \pm 2.2$  years with MD trend analysis.

## Discussion

The reliability (consistency) and sensitivity of the binomial PLR in detecting VF progression was analyzed through HFA 10-2 tests on 196 eyes of 103 patients with RP, and compared with those of MD trend analysis and the PoPLR method. A Kaplan–Meier survival analysis and a log rank test revealed that binomial PLR detected VF progression significantly earlier than the other two methods. However, a possible caveat remains that the earlier detection of progression with the binomial PLR is because of detecting falsely too many progressions. We conducted the PBP, PBNP, and PIP analyses shedding light on this issue, and, as a result, these values were not significantly different among the three approaches. These findings suggest that the binomial PLR detect progression significantly earlier than MD trend analysis and the PoPLR method without sacrificing the accuracy (reliability).

The reliability (consistency) of the diagnosis with each method (i.e., binomial PLR, MD trend analysis, and PoPLR) was investigated by comparing the diagnosis with VF<sub>1-10</sub> and those with shorter VF sequences. This is because the VF continuously progresses in RP and the diagnosis should not be changed over time, once diagnosed as progressive. In our previous study,<sup>20</sup> we evaluated the PBP, PBNP,

and PIP through binomial PLR, PoPLR, and MD trend analysis in cases of glaucomatous eyes, using the HFA 10-2 test. The PBP, PBNP, and PIP values of binomial PLR were not significantly different from those of PoPLR and MD trend analysis. The current results on tests of eyes with RP agree with these results, suggesting that binomial PLR is a reliable method of evaluating VF progression in the central 10°, not only in eyes with glaucoma, but also those with RP. Furthermore, similar to the results of our studies of glaucomatous eyes,<sup>16,20</sup> Kaplan–Meier survival analyses indicated that binomial PLR detected VF progression significantly earlier than PoPLR and MD trend analysis, suggesting that binomial PLR is useful in the early detection of VF progression in RP eyes as well. PoPLR was developed to disclose the progression of the entire VF in glaucomatous eyes at an earlier stage, compared with the MD trend analysis.<sup>14</sup> The current results suggest that this technique is also useful in eyes with RP, but that there remains a greater advantage with the binomial PLR method. In contrast, a possible associated caveat is that the binomial PLR method has not been readily useable in the clinical setting. It would be clinically beneficial to develop software and support tools to detect VF progression, as introduced in this study, similar to PROGRESSOR (Medisoft, Inc., London, UK).<sup>23</sup>

The binomial PLR method analyzes the results of PLR, which uses linear regression analysis. A case could be made for applying a nonlinear regression analysis, such as an exponential model.<sup>24,25</sup> However, we have shown that linear regression outperforms nonlinear regression in predicting future VF, using the HFA 24-2 test in glaucoma.<sup>8,26–28</sup> Moreover, we recently investigated the use of nonlinear regression models using the HFA 10-2 test, and concluded that they showed no advantage over the conventional linear regression method.<sup>26,29,30</sup> Besides, a non-negligible problem associated with a nonlinear regression analysis such as the exponential model is that *P* values cannot be calculated; thus, the binomial PLR method cannot be applied. These results support the view that it would be advantageous to apply binomial tests to PLR, not nonlinear regressions, in glaucoma and also in RP.

The accurate and early detection of VF progression is important in RP management, because the extent of the defects in the VF is related directly to the quality of vision in patients with RP.<sup>1,31</sup> As suggested in a previous study, visual disability is closely associated with HFA 10-2 test results.<sup>5</sup> The current results suggest that the application of the binomial PLR method to the HFA 10-2 test will aid the estimation of patients' future condition. In addition, considering the difficulty that remains in devising a treatment strategy to

alleviate the progression of RP, the accurate assessment of VF progression is important for the establishment of treatment. Some clinicians prescribe oral vitamin A to patients with RP; however, the treatment outcomes varied across the studies.<sup>32–35</sup> Docosahexaenoic acid, an omega-3 fatty acid highly present in oily fish, has also been proposed as an additional nutritional treatment, but its effectiveness remains uncertain.<sup>35–40</sup> One possible reason for these contradictory results is that the assessments of visual function differed across the studies.<sup>41</sup> For instance, visual acuity was often used in the assessment of visual function. However, visual acuity merely reflects the retinal function around the fovea and tends to be insensitive to the severity of disease.<sup>42</sup> For instance, we previously developed a model to predict VF sensitivity measured with the HFA 10-2 test using visual acuity in RP.<sup>19</sup> The study revealed that the model improved when the assessment of the structural damage demonstrated with fundus autofluorescence imaging was combined, implying the limitation of using visual acuity in establishing the severity of disease in RP. The current results suggest that the binomial PLR method will be useful in assessing VF progression with the HFA 10-2 test when evaluating the effects of any candidate treatment.

There are several limitations in the current study. First, we did not consider the patients' genetic information. Recently, owing to gene-specific approaches including gene therapy, genetic information is of growing interest in the management of RP. For instance, variants in many genes, such as *ABCA4*,<sup>43</sup> *PRPH2*,<sup>44,45</sup> and *PROM1*<sup>46</sup> genes, are associated with various phenotypes. Owing to its retrospective nature, no genetic information was included in this study. Thus, the evaluation of VF progression with certain genetically defined forms of RP remains to be investigated in a future study. Second, the PBP, PBNP, and PIP were calculated with VF<sub>1–10</sub> as a surrogate for the absolute true progression. The absolute true progression cannot be stated. Thus, the current study may require validation using a simulation dataset. In the current study, we hypothesized the linear regression at each test point. This assumption was based on our previous report that linear regression was most suitable in glaucomatous eyes<sup>26</sup>; however, this point needs further investigation, specifically in RP. We limited our analysis to static perimetry measures because the process to standardize and equate static and kinetic VF measures for this application would require additional extensive modeling. Previously, we reported that microperimetry with fundus tracking (MP-3, Nidek Co. Ltd, Gamagori, Japan) demonstrated a better structure–function relationship in glaucomatous eyes than did HFA.<sup>47</sup> Based on the current study's results,

the application of a PLR method to the results of microperimetry may also achieve improved assessments in central VF progression in RP. This point remains to be investigated in a future study. Similarly, future studies should concentrate on comparisons of the usefulness of the proposed approach and other nonstandard VAs, such as low luminance VA and contrast sensitivity.<sup>48,49</sup>

In conclusion, we applied a binomial test to the PLR analysis of the HFA 10-2 test of eyes with RP, and revealed that binomial PLR achieved reliable and earlier detection of VF progression.

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## References

- Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *Lancet*. 2006;368:1795–1809.
- Narayan DS, Wood JP, Chidlow G, Casson RJ. A review of the mechanisms of cone degeneration in retinitis pigmentosa. *Acta Ophthalmol*. 2016;94:748–754.
- Abe K, Iijima H, Hirakawa H, Tsukahara Y, Toda Y. Visual acuity and 10 automated static perimetry in eyes with retinitis pigmentosa. *Jpn J Ophthalmol*. 2002;46:581–585.
- Swanson WH, Feliuss J, Birch DG. Effect of stimulus size on static visual fields in patients with retinitis pigmentosa. *Ophthalmology*. 2000;107:1950–1954.
- Sumi I, Matsumoto S, Okajima O, Shirato S. The relationship between visual disability and visual scores in patients with retinitis pigmentosa. *Jpn J Ophthalmol*. 2000;44:82–87.
- Wild JM, Hussey MK, Flanagan JG, Trope GE. Pointwise topographical and longitudinal modeling of the visual field in glaucoma. *Invest Ophthalmol Vis Sci*. 1993;34:1907–1916.
- Azarbod P, Mock D, Bitrian E, et al. Validation of point-wise exponential regression to measure the decay rates of glaucomatous visual fields. *Invest Ophthalmol Vis Sci*. 2012;53:5403–5409.
- McNaught AI, Crabb DP, Fitzke FW, Hitchings RA. Modelling series of visual fields to detect progression in normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 1995;233:750–755.
- Viswanathan AC, Crabb DP, McNaught AI, et al. Interobserver agreement on visual field progression in glaucoma: a comparison of methods. *Br J Ophthalmol*. 2003;87:726–730.
- Viswanathan AC, Fitzke FW, Hitchings RA. Early detection of visual field progression in glaucoma: a comparison of PROGRESSOR and STATPAC 2. *Br J Ophthalmol*. 1997;81:1037–1042.
- Nouri-Mahdavi K, Brigatti L, Weitzman M, Caprioli J. Comparison of methods to detect visual field progression in glaucoma. *Ophthalmology*. 1997;104:1228–1236.
- Yousefi S, Kiwaki T, Zheng Y, et al. Detection of longitudinal visual field progression in glaucoma using machine learning. *Am J Ophthalmol*. 2018;193:71–79.
- Karakawa A, Murata H, Hirasawa H, Mayama C, Asaoka R. Detection of progression of glaucomatous visual field damage using the pointwise method with the binomial test. *PLoS One*. 2013;8:e78630.
- O’Leary N, Chauhan BC, Artes PH. Visual field progression in glaucoma: estimating the overall significance of deterioration with permutation analyses of pointwise linear regression (PoPLR). *Invest Ophthalmol Vis Sci*. 2012;53:6776–6784.
- Asano S, Murata H, Matsuura M, Fujino Y, Asaoka R. Early detection of glaucomatous visual field progression using Pointwise linear regression with binomial test in the central 10 degrees. *Am J Ophthalmol*. 2019;199:140–149.
- Asano S, Murata H, Matsuura M, et al. Validating the efficacy of the binomial pointwise linear regression method to detect glaucoma progression with multicentral database. *Br J Ophthalmol*. 2020;104:569–574.
- da Cruz L, Dorn JD, Humayun MS, et al. Five-year safety and performance results from the Argus II retinal prosthesis system clinical trial. *Ophthalmology*. 2016;123:2248–2254.



18. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017;390:849–860.
19. Inoue T, Nakajima K, Hashimoto Y, et al. A prediction method of visual field sensitivity using fundus autofluorescence images in patients with retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2020;61:51.
20. Asano S, Murata H, Matsuura M, Fujino Y, Asaoka R. Early detection of glaucomatous visual field progression using pointwise linear regression with binomial test in the central 10 degrees. *Am J Ophthalmol*. 2018;199:140–149.
21. van de Wiel MA, Berkhof J, van Wieringen WN. Testing the prediction error difference between 2 predictors. *Biostatistics*. 2009;10:550–560.
22. Fisher RA. Statistical methods for research workers. *Breakthroughs in statistics*. New York: Springer; 1992:66–70.
23. Fitzke FW, Hitchings RA, Poinoosawmy D, McNaught AI, Crabb DP. Analysis of visual field progression in glaucoma. *Br J Ophthalmol*. 1996;80:40–48.
24. Caprioli J, Mock D, Bitrian E, et al. A method to measure and predict rates of regional visual field decay in glaucoma. *Invest Ophthalmol Vis Sci*. 2011;52:4765–4773.
25. Mikelberg FS, Schulzer M, Drance SM, Lau W. The rate of progression of scotomas in glaucoma. *Am J Ophthalmol*. 1986;101:1–6.
26. Taketani Y, Murata H, Fujino Y, Mayama C, Asaoka R. How many visual fields are required to precisely predict future test results in glaucoma patients when using different trend analyses? *Invest Ophthalmol Vis Sci*. 2015;56:4076–4082.
27. Bengtsson B, Patella VM, Heijl A. Prediction of glaucomatous visual field loss by extrapolation of linear trends. *Arch Ophthalmol*. 2009;127:1610–1615.
28. Russell RA, Malik R, Chauhan BC, Crabb DP, Garway-Heath DF. Improved estimates of visual field progression using Bayesian linear regression to integrate structural information in patients with ocular hypertension. *Invest Ophthalmol Vis Sci*. 2012;53:2760–2769.
29. Fujino Y, Murata H, Mayama C, Asaoka R. Applying "Lasso" regression to predict future visual field progression in glaucoma patients. *Invest Ophthalmol Vis Sci*. 2015;56:2334–2339.
30. Fujino Y, Murata H, Mayama C, Matsuo H, Asaoka R. Applying "Lasso" regression to predict future glaucomatous visual field progression in the central 10 degrees. *J Glaucoma*. 2017;26:113–118.
31. Holopigian K, Greenstein V, Seiple W, Carr RE. Rates of change differ among measures of visual function in patients with retinitis pigmentosa. *Ophthalmology*. 1996;103:398–405.
32. Berson EL. Treatment of retinitis pigmentosa with vitamin A. *Digit J Ophthalmol*. 1998;4:1–4.
33. Berson EL, Rosner B, Sandberg MA, et al. vitamin A supplementation for retinitis pigmentosa. *Arch Ophthalmol*. 1993;111:1456–1458.
34. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol*. 1993;111:761–772.
35. Schwartz SG, Wang X, Chavis P, Kuriyan AE, Abariga SA. Vitamin A and fish oils for preventing the progression of retinitis pigmentosa. *Cochrane Database Syst Rev*. 2020;6:CD008428.
36. Berson EL, Rosner B, Sandberg MA, et al. Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin a treatment: subgroup analyses. *Arch Ophthalmol*. 2004;122:1306–1314.
37. Berson EL, Rosner B, Sandberg MA, et al. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin a treatment. *Arch Ophthalmol*. 2004;122:1297–1305.
38. Hoffman DR, Hughbanks-Wheaton DK, Pearson NS, et al. Four-year placebo-controlled trial of docosahexaenoic acid in X-linked retinitis pigmentosa (DHAX trial): a randomized clinical trial. *JAMA Ophthalmol*. 2014;132:866–873.
39. Hoffman DR, Hughbanks-Wheaton DK, Spencer R, et al. Docosahexaenoic acid slows visual field progression in X-linked retinitis pigmentosa: ancillary outcomes of the DHAX trial. *Invest Ophthalmol Vis Sci*. 2015;56:6646–6653.
40. Hoffman DR, Locke KG, Wheaton DH, Fish GE, Spencer R, Birch DG. A randomized, placebo-controlled clinical trial of docosahexaenoic acid supplementation for X-linked retinitis pigmentosa. *Am J Ophthalmol*. 2004;137:704–718.
41. Schwartz SG, Wang X, Chavis P, Kuriyan AE, Abariga SA. Vitamin A and fish oils for preventing the progression of retinitis pigmentosa. *Cochrane Database Syst Rev*. 2020;6:CD008428.
42. Menghini M, Cehajic-Kapetanovic J, MacLaren RE. Monitoring progression of retinitis pigmentosa: current recommendations and recent advances. *Expert Opin Orphan Drugs*. 2020;8:67–78.
43. Cornelis SS, Bax NM, Zernant J, et al. In silico functional meta-analysis of 5,962 ABCA4



- variants in 3,928 retinal dystrophy cases. *Hum Mutat.* 2017;38:400–408.
44. Boon CJ, den Hollander AI, Hoyng CB, Cremers FP, Klevering BJ, Keunen JE. The spectrum of retinal dystrophies caused by mutations in the peripherin/RDS gene. *Prog Retin Eye Res.* 2008;27:213–235.
  45. Cehajic-Kapetanovic J, Birtel J, McClements ME, et al. Clinical and molecular characterization of PROM1-related retinal degeneration. *JAMA Netw Open.* 2019;2:e195752.
  46. Fujinami K, Oishi A, Yang L, et al. Clinical and genetic characteristics of 10 Japanese patients with PROM1-associated retinal disorder: a report of the phenotype spectrum and a literature review in the Japanese population. *Am J Med Genet C Semin Med Genet.* 2020;184:656–74.
  47. Matsuura M, Murata H, Fujino Y, Hirasawa K, Yanagisawa M, Asaoka R. Evaluating the usefulness of MP-3 microperimetry in glaucoma patients. *Am J Ophthalmol.* 2018;187:1–9.
  48. Fujita K, Shinoda K, Matsumoto CS, et al. Low luminance visual acuity in patients with central serous chorioretinopathy. *Clin Exp Optom.* 2013;96:100–105.
  49. Richman J, Spaeth GL, Wirostko B. Contrast sensitivity basics and a critique of currently available tests. *Journal of Cataract & Refractive Surgery.* 2013;39:1100–1106.