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# Ocular biometry with swept-source optical coherence tomography-based optical biometer in Japanese patients with *EYS*-related retinitis pigmentosa: a retrospective study

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## Abstract

**Background:** This study aimed to identify the features of ocular biometry in patients with *EYS*-related retinitis pigmentosa using IOLMaster 700.

**Methods:** We retrospectively reviewed the medical records of patients with retinitis pigmentosa. Patients with records of the following were included: (1) ocular biometry measurements using the IOLMaster 700 and (2) genetic diagnostic tests. Axial length, keratometry, anterior chamber depth, aqueous depth, lens thickness, central corneal thickness (CCT), and corneal diameter (white to white) measurements were extracted. Based on keratometry measurements, (1) standard keratometric astigmatism, (2) posterior corneal astigmatism, and (3) total corneal astigmatism were obtained. Demographics and biometric parameters were compared between patients with *EYS*-related retinitis pigmentosa and other patients with retinitis pigmentosa.

**Results:** A total of 86 eyes of 44 patients (23 females and 21 males; mean age: 47.7 years) with retinitis pigmentosa were included. Of these, 18 were identified as having *EYS* variants. CCT was significantly thinner ( $P < 0.001$ ) and the posterior corneal curvature at the steepest meridian was significantly smaller ( $P = 0.024$ ) in patients with *EYS*-related retinitis pigmentosa than in other patients with retinitis pigmentosa. The magnitudes of all corneal astigmatism measurements was higher in patients with *EYS*-related RP, although these differences were not statistically significant.

**Conclusion:** Patients with *EYS*-related retinitis pigmentosa had unique features in ocular biometry, such as thinner central corneal thickness and smaller posterior corneal curvature radius at the steepest meridian compared with other patients with retinitis pigmentosa. The findings suggest that patients with retinitis pigmentosa have different ocular dimension features among the different causative genes.

**Keywords:** Retinitis pigmentosa, Ocular biometry, Causative genes, *EYS*, Astigmatism, Keratometry

## Background

Retinitis pigmentosa (RP) is the most common hereditary retinal dystrophy, with a worldwide prevalence of approximately 1 in 4000 individuals [1]. The clinical

course of RP is characterized by night blindness and progressive loss of visual field due to degeneration of photoreceptors. RP has been reported to affect not only the retina but also the ocular dimensions [2, 3]. The alterations in ocular dimensions in patients with RP could be associated with a high prevalence of keratoconus [4], angle-closure glaucoma [5], and certain refractive errors, such as myopia and astigmatism [6]. Although there are

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a few reports that describe the alterations in the anterior segment [2, 3], detailed ocular biometry in patients with RP is not yet fully understood.

The IOLMaster 700 (Carl Zeiss AG, Oberkochen, Germany) is the first swept-source optical coherence tomography (OCT)-based biometry device that provides anatomical details of the complete longitudinal section of the eye; all axial measurements including axial length, central corneal thickness (CCT), anterior chamber depth (ACD), and lens thickness can be obtained. Additionally, it combines telecentric keratometry and OCT technology to measure both anterior and posterior corneal curvatures.

Recently, accumulated knowledge of genetic findings in RP has shown various clinical features among different causative genes. Some causative genes have specific pathological conditions complicated with the retinal dystrophy, for example, high myopia in *RPGR* variants [7] or angle-closure glaucoma in *CRB1* and *MFRP* variants [8–10]. These reports have suggested that patients with RP may also have different alterations in ocular dimensions among different causative genes. In the Japanese population, the most prevalent causative gene is *EYS*, which accounts for 30% of genetically solved cases [11–14]. Thus, it is the most promising causative gene for which clinical data are being accumulated in Japan. To the best of our knowledge, this is the first study to describe the ocular dimension features of patients with *EYS*-related RP. This pilot study aimed to investigate the hypothesis that different causative genes are associated with different ocular biometry findings, by identifying the features of IOLMaster 700-based total ocular biometry in patients with *EYS*-related RP.

## Materials and methods

This retrospective study included patients diagnosed with RP who were followed up at the Kobe City Eye Hospital between June 2020 and December 2020. RP was diagnosed according to the guidelines of the Japanese Ophthalmological Society [15], based on clinical history, fundus appearance, visual fields, and full field electroretinogram results. Cataract was defined as the presence of nuclear (greater than grade 1 of Emery-Little classification), cortical, or posterior subcapsular (PSC) cataract. The data related to the presence or absence of cataract were retrieved from the medical records as recorded by one or more of the three ophthalmologists who were in charge of the inherited retinal disease clinic of our hospital. The patients were included in the study only if the medical records had ocular biometry measurements with the IOLMaster 700 and genetic diagnostic tests. Patients with a history of ocular surgery, including cataract extraction, corneal or other anterior segment diseases

that could lead to corneal opacification, or astigmatism were excluded from the study. Among the 44 patients who met these criteria, genetic diagnostic tests identified *EYS* variants in 18, *USH2A* variants in 4, and other gene variants in 11 patients. Eleven cases remained genetically unsolved with our multi gene-panel analysis as described in the later section “Genetic analysis”. The genetic diagnoses of the patients are shown in Table 1. Following this distribution of causative genes, we planned to use the clinical data of patients with variants other than *EYS* as the control group. None of the patients had causative genes that could affect ocular biometry, such as *RPGR*, *CRB1*, and *MFRP*. We divided the patients into two groups: *EYS*-related RP (35 eyes of 18 patients with *EYS* variants) and other RP (51 eyes of 26 patients with other variants and genetically unsolved cases). Genetic variants in the patients with *EYS*-related RP included in this study are presented in Additional file 1.

## Ocular biometry using the IOLMaster 700

Biometric measurements were performed before pupillary dilatation in all patients. The records of all measurements, including axial length, keratometry, CCT, ACD, aqueous depth, lens thickness, and corneal diameter (white to white), were extracted. ACD is the distance between the tear film and the anterior lens capsule, and aqueous depth is the distance between the corneal endothelium and anterior lens capsule. Total keratometry is a new measurement that combines telecentric keratometry and OCT technology. In addition to standard keratometry in which the corneal curvature radius at the flattest meridian (R1) and steepest meridian (R2) is

**Table 1** Genetic diagnosis of patients with retinitis pigmentosa

Genetic variants	Number of patients
<i>EYS</i>	18
<i>USH2A</i>	4
<i>PDE6B</i>	1
<i>RPE65</i>	1
<i>C2orf71</i>	1
<i>MAK</i>	1
<i>PRPF31</i>	1
<i>PROM1</i>	1
<i>NHPH1</i>	1
<i>RHO</i>	1
<i>NRL</i>	1
<i>IMPDH</i>	1
<i>TOPORS</i>	1
Genetically unsolved	11

measured, posterior corneal surface measurements (PR1 and PR2) and total keratometry reading (TR1 and TR2) can be obtained.

### Corneal astigmatism measurements

We analysed three corneal astigmatism values based on keratometry measurements: (1) standard keratometric astigmatism (KA), (2) posterior corneal astigmatism (PCA), and (3) total corneal astigmatism (TCA) [16]. The following formulae were used:

(1) Standard KA  $(1.3375-1) \times 1000 / R2 - (1.3375-1) \times 1000 / R1$ .

The keratometric refractive index of 1.3375 was used to convert R into corneal power. (2) PCA  $(1.336-1.376) \times 1000 / PR2 - (1.336-1.376) \times 1000 / PR1$ . The refractive indices of the cornea and aqueous humour were 1.336 and 1.376, respectively, and were used to convert PR into corneal power. (3) TCA.  $(1.3375-1) \times 1000 / TR2 - (1.3375-1) \times 1000 / TR1$  The keratometric refractive index of 1.3375 was used to convert TR into corneal power

### Genetic analysis

Genetic testing was performed by stepwise Sanger-sequencing using one or two panels of 15 and 27 genes in 2008–2015 [13] or next-generation sequencing using panels of 39 or 50 genes in 2015–2019 [17] or 2019 and later [18], respectively. The patients in this study underwent one of these screenings for genetic diagnosis tests.

### Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 25 (SPSS Inc., Chicago, IL, USA). The demographics and biometric parameters of *EYS*-related RP and other RP were compared. The normality of the data distribution was tested using the Kolmogorov–Smirnov test; age and WTW were non-normally distributed. Differences in age were compared using the Mann–Whitney U test. The ratio of female to male patients was compared using the chi-square test. A generalized estimating equation model was used for other variables to account for the correlation between both eyes of a single patient. Statistical significance was set at  $P < 0.05$ .

### Results

A total of 86 eyes of 44 patients (21 males and 23 females) with RP were included. The demographic data and ocular biometric parameters of the patients are summarised in Table 2. The mean median age (interquartile range) was 51.0 (20.0) years (range: 21–68 years). There were 51 eyes with clear lenses and 45 eyes with cataracts (including

13 eyes with PSC). Eyes with intraocular lenses were excluded from the study.

A comparison between patients with *EYS*-related RP and those with other RP is also shown in Table 2. There was no significant difference in sex and the presence of cataract between the two groups. The frequency of PSC was significantly higher in patients with *EYS*-related RP (28.6%) than in those with other RP (5.9%) ( $P = 0.045$ ). CCT was significantly thinner in patients with *EYS*-related RP than in those with other RP ( $P < 0.001$ ). In posterior keratometry, corneal curvature radius at the steepest meridian was significantly smaller in patients with *EYS*-related RP ( $P = 0.024$ ). In standard and total keratometry, corneal curvature radius at the steepest meridian (R2 and TR2) was smaller in patients with *EYS*-related RP, although these differences were not statistically significant. The magnitudes of all corneal astigmatism measurements, namely standard KA, PCA, and TCA, were greater in patients with *EYS*-related RP, although these differences were not statistically significant.

### Discussion

This study presents the total ocular biometry measurements in Japanese patients with RP. We observed some unique features of ocular dimensions in patients with *EYS*-related RP. First, CCT was thinner in patients with *EYS*-related RP than in those with other RP. Second, corneal curvature radius at the steepest meridian was smaller in patients with *EYS*-related RP than in those with other RP. Küçük et al. have reported that Turkish patients with RP had thinner CCT (mean: 518  $\mu$ m), higher maximum keratometry values [mean: 45.85 D (equivalent to a corneal curvature radius of 7.36 mm)], and smaller anterior chamber angle on Scheimpflug imaging compared to those of healthy controls [mean CCT: 534  $\mu$ m, mean maximum keratometry: 44.69 D (equivalent to a corneal curvature radius of 7.55 mm)]. They suggested that patients with RP may have different anterior segment parameters compared with healthy subjects; however, genetic information was not presented [3]. In our study, the patients with *EYS*-associated RP had thinner CCT and higher maximum keratometry values, as also reported by Küçük et al., than the patients with other RP. Our results suggest that these unique features in patients with RP are associated with causative genes, such as *EYS*. Furthermore, the above-mentioned corneal alterations could be associated with astigmatism. A previous study on corneal astigmatism measurement using the IOLMaster 700 in the Chinese population reported a mean standard KA of 1.00 D, mean PCA of -0.19 D, and mean TCA of 1.03 D [16], all of which are smaller in magnitude compared to those of our patients

**Table 2** Patient demographics and ocular biometric parameters

	Overall	EYS-related RP	Other RP	P value*
	44 patients	18 patients	26 patients	
Age (years), median [IQR]	51.0 [20.0]	49.5 [18.0]	51.0 [29.0]	0.748
Female, n (%)	23 (52.3)	12 (66.7)	11 (42.3)	0.112
	86 eyes	35 eyes	51 eyes	
Cataract, n (%)	45 (52.3)	19 (54.3)	26 (51.0)	0.829
PSC, n (%)	13 (15.1)	10 (28.6)	3 (5.9)	0.045*
<b>Biometric parameters<sup>a</sup></b>				
AL (mm)	24.2 (23.9–24.5)	24.3 (23.8–24.8)	24.1 (23.9–24.4)	0.610
CCT (μm)	526.0 (520.6–531.4)	515.4 (506.9–523.9)	536.6 (529.8–543.4)	<0.001*
ACD (mm)	3.05 (2.98–3.13)	3.05 (2.92–3.17)	3.06 (2.98–3.14)	0.861
AQD (mm)	2.53 (2.45–2.60)	2.53 (2.40–2.66)	2.52 (2.44–2.61)	0.922
LT (mm)	4.48 (4.39–4.57)	4.53 (4.38–4.67)	4.44 (4.32–4.55)	0.357
WTW (mm)	12.1 (12.0–12.1)	12.1 (12.0–12.2)	12.0 (11.9–12.1)	0.349
<b>Keratometry</b>				
R1 (mm)	7.84 (7.79–7.89)	7.82 (7.74–7.89)	7.87 (7.80–7.93)	0.316
R2 (mm)	7.56 (7.51–7.61)	7.52 (7.43–7.60)	7.61 (7.56–7.66)	0.072
PR1 (mm)	6.99 (6.94–7.04)	6.96 (6.88–7.04)	7.02 (6.96–7.08)	0.208
PR2 (mm)	6.61 (6.56–6.67)	6.55 (6.45–6.65)	6.68 (6.63–6.73)	0.024*
TR1 (mm)	7.83 (7.78–7.88)	7.81 (7.74–7.88)	7.86 (7.80–7.92)	0.331
TR2 (mm)	7.57 (7.52–7.62)	7.52 (7.44–7.61)	7.61 (7.55–7.67)	0.102
<b>Astigmatism</b>				
Standard KA (D)	1.59 (1.40–1.78)	1.75 (1.44–2.06)	1.43 (1.22–1.64)	0.093
PCA (D)	-0.33 (-0.37 to -0.29)	-0.37 (-0.42 to -0.31)	-0.29 (-0.34 to -0.25)	0.061
TCA (D)	1.52 (1.33–1.70)	1.65 (1.35–1.96)	1.38 (1.18–1.58)	0.145

Abbreviations: RP, retinitis pigmentosa, IQR, interquartile range, PSC, posterior subcapsular cataract, AL, axial length, CCT, central corneal thickness, ACD, anterior chamber depth, AQD, aqueous depth, LT, lens thickness, WTW, white to white, R1 and R2, standard keratometry corneal curvature radius at the flattest and steepest meridians, respectively, PR1 and PR2, posterior corneal curvatures radius at the flattest and steepest meridian, respectively, TR1 and TR2, total keratometry corneal curvature radius at the flattest and steepest meridians respectively KA, keratometric astigmatism PCA, posterior corneal astigmatism TCA, total corneal astigmatism

\* Statistically significant at the  $P < 0.05$  level (generalized estimating equation model)

<sup>a</sup> Eye-level values are represented as the estimated marginal mean (95% confidence interval)

(mean standard KA: 1.59 D, mean PCA: -0.33 D, and mean TCA: 1.52 D). The greater magnitude of corneal astigmatism may contribute to the reported high prevalence of astigmatism in patients with RP [6], especially in patients with EYS-related RP, as observed in our cohort.

The mechanism of corneal alteration in patients with RP has not yet been explained. RP has been reported as a risk factor for keratoconus, which is characterized by progressive thinning of the cornea [19]. Low-grade inflammation during the course of retinal degeneration in RP is considered the pathological mechanism underlying keratoconus. PSC is the most common subtype of RP-related cataracts, and inflammation also plays a major role in the formation of PSC in RP [20]. In our cohort, 15.1% of patients had PSC, and its prevalence was higher in patients with EYS-related RP (28.6%) than in those with other RP (5.9%), suggesting that the severity of inflammation may contribute to different degrees of corneal alteration in RP.

EYS variants were first reported to have a pathogenic effect on RP in 2008 [21, 22]. It has four isoforms all of which are mainly expressed in the human retina; however, its expression in the cornea has not yet been reported. The EYS protein is considered to play a role in maintaining the stability of the ciliary axoneme in photoreceptors [23]. To date, there are no findings that explain the association between the EYS variant and corneal alterations. Future studies are needed to understand the underlying mechanisms of our results.

To the best of our knowledge, this is the first report to describe the ocular dimension features of patients with EYS-related RP. A major limitation of this study was that each of the genetic variants other than EYS had a small sample size, which limits our ability to understand their respective characteristics. Another limitation was the retrospective nature of the study design. Additionally, statistical analysis of the comparison between RP eyes and normal eyes was lacking because

we did not have a control group of normal subjects in this study. Finally, we used different panels for genetic testing. Using older methods might contribute to detection failure of some causative genes; however, *EYS* was included in all the panels we used. Further studies including a large number of patients and a control group are required to validate the unique findings of ocular biometry in patients with RP.

In conclusion, patients with *EYS*-related RP had some unique features of ocular dimensions, such as thinner CCT and smaller posterior corneal curvature radius at the steep meridian compared to patients with other RP. The preliminary results of this study suggest that patients with RP have different ocular dimension features among the different causative genes.

#### Abbreviations

ACD: Anterior chamber depth; AQD: Aqueous depth; CCT: Central corneal thickness; KA: Keratometric astigmatism; LT: Lens thickness; OCT: Optical coherence tomography; PCA: Posterior corneal astigmatism; PR1: Posterior corneal curvature radius at the flattest meridian; PR2: Posterior corneal curvature radius at the steepest meridian; PSC: Posterior subcapsular cataract; RP: Retinitis pigmentosa; R1: Corneal curvature radius at the flattest meridian; R2: Corneal curvature radius at the steepest meridian; TCA: Total corneal astigmatism; TR1: Total keratometry corneal curvature radius at the flattest meridian; TR2: Total keratometry corneal curvature radius at the steepest meridian; WTW: White to white.

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12886-022-02284-3>.

**Additional file 1: Supplementary Table 1.** Description of data: Genetic variants in the patients with *EYS*-related retinitis pigmentosa.

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#### Authors' contributions

DS, SY, AM, and YH contributed to the study conception, study design, and drafting of this manuscript. MN and YK reviewed the manuscript critically. All authors have read and approved the final manuscript.

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#### Availability of data and materials

All data included in this study are available from the corresponding author upon request.

#### Declarations

##### Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Kobe City Medical Center General Hospital (Kobe, Japan). Written informed consent was obtained from all participants. We applied the opt-out method to obtain informed consent for this observational study involving the use of medical records. Patients who did not give their consent were excluded.

#### Consent for publication

Not applicable

#### Competing interests

The authors declare that they have no competing interests.

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