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RETINAL DISORDERS

Outer retinal layers as predictors of visual acuity in retinitis pigmentosa: a cross-sectional study

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Abstract

Purpose To evaluate the integrity of the outer retinal layers—outer nuclear layer (ONL), external limiting membrane (ELM), ellipsoid (EZ), and interdigitation band (IZ)—using spectral-domain optical coherence tomography and estimate their effect on visual acuity in retinitis pigmentosa (RP).

Methods A cross-sectional study was performed in the Ophthalmology Department of Hospital de Braga, Portugal. Patients with RP followed in the Hospital de Braga during January to August 2017 were included. Exclusion criteria were lack of data, macular edema due to RP, and concomitant retinal, optic nerve, or corneal disease that could interfere with visual acuity. Age, sex, time from diagnosis, phakic status, ONL thickness, and presence or absence of foveal ELM, EZ, and IZ were correlated to the best-corrected visual acuity (BCVA).

Results Forty-eight eyes were analyzed. There was a strong and positive correlation in BCVA between both eyes ($p < .001^*$). ONL thickness was decreased in 95.8%. The EZ was the most absent layer (79.2%), followed by IZ (70.8%) and ELM (45.8%). A positive family history ($p = .04^*$) and increased time from diagnosis ($p = .037^*$) correlated with worse BCVA. A thicker ONL ($p = .001^*$) and the presence of subfoveal ELM ($p < .001^*$), EZ ($p < .001^*$), and IZ ($p = .02^*$) are correlated with better BCVA. There was a strong and positive correlation between the number of layers affected and a lower BCVA ($p < .001$). The presence of EZ was a significant predictor of BCVA ($p = .02^*$).

Conclusions The status of the outer retinal layers seems to influence BCVA. The status of the EZ was the most important predictor of BCVA but the ONL, ELM, and IZ may have a cumulative effect in the progression of visual loss.

Keywords Retinitis pigmentosa · SD-OCT · Outer nuclear layer · External limiting membrane · Ellipsoid band · Interdigitation band

Introduction

Retinitis pigmentosa (RP) refers to a wide and heterogeneous group of inherited retinal diseases, being one of the causes of acquired irreversible blindness in developed countries [1–4]. This family of diseases is characterized by progressive degeneration of the retinal pigment epithelium (RPE), apoptosis of the photoreceptors, attenuation of the retinal vessels, sclerosis, and atrophy of the choriocapillaris [5–9]. These alterations are responsible for the early onset of nyctalopia, progressive

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peripheral visual field loss, and gradual deterioration of central visual acuity that characterize RP [10]. Although the diagnosis of RP can be made based on clinical presentation, different ancillary tests such as visual fields, wide-field autofluorescence, electroretinography, and genetic investigation have been used to document the clinical evolution of this condition [2, 4, 10].

Spectral-domain optical coherence tomography (SD-OCT) is a non-invasive tool, sensitive and indispensable for observing the microstructures of the outer retinal layers [8, 11, 12]. On macular SD-OCT, RP is characterized by alterations of the photoreceptors inner/outer segment (IS/OS) junction and the external limiting membrane (ELM) [4]. Using time-domain OCT, the length or the presence of the ellipsoid band (EZ) (previously known as the IS/OS line) was significantly correlated with visual acuity in RP [13, 14]. The outer nuclear layer (ONL) contains the photoreceptor cell bodies, which because of their direct relationship to visual function are a critical biomarker of macular diseases [15]. Menghini et al. correlated the diminished ONL thickness and low cone density in RP. However, only 12 eyes with RP were included and the ONL measurements were perifoveal [16]. Matsuo et al. described an association with a poor visual outcome when the surface of nerve fiber layer, the inner plexiform layer, and the outer plexiform layer were affected in the disease process. However, these authors did not address how the changes in the different outer retinal layers may affect the visual function in this disease. It is known for several macular diseases that the status of the outer retinal layers may have a strong correlation with visual acuity [8]. Even though the defects of the outer retinal layers can be identified on SD-OCT (outer nuclear layer (ONL), external limiting membrane (ELM), ellipsoid (EZ), and interdigitation bands (IZ)), their relationship to visual acuity still needs to be further evaluated in RP. The main objectives of this study are to evaluate the changes of the outer retinal layers in RP and to investigate its potential repercussions on visual acuity.

Methods

This cross-sectional study was conducted at the Ophthalmology Department of Hospital de Braga, Portugal, and was approved by the institutional review committee and adhered to the tenets of the Declaration of Helsinki. An anonymized extraction of medical records and SD-OCT of patients with retinitis pigmentosa who presented between January and August 2017 were evaluated. All participants underwent a comprehensive non-invasive eye exam performed at the Ophthalmology Department of Hospital de Braga. Date of diagnosis, familiar RP affection, age, and gender were registered. Examination included best-corrected visual acuity (BCVA) using decimal scale charts that was later converted to the logarithm of the minimum angle of resolution (logMAR), slit-lamp biomicroscopy, and a dilated fundus examination. The diagnosis of RP was made clinically from funduscopic examination. All patients performed funduscopic examination, retinography, and SD-OCT. Inclusion criteria included a diagnosis of RP and clear media to allow for optimal OCT examination. This included pseudophakic patients as many patients with RP develop early posterior subcapsular cataract and had been submitted to cataract surgery [17]. Patients with macular edema associated with the RP were excluded. Other exclusion criteria included patients with cataract, vitreous opacities, poor image quality or any other retinal, and optic nerve or cornea pathology as lack of data to continue the study.

Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) was used to measure retinal thickness and evaluate the outer retinal bands. The technique consisted in obtaining a macular square (20 × 20°), centered on the fovea, composed of 25 horizontal and vertical B-scans, and spaced at 240 μm. Two high-quality, horizontal and vertical line scans centered on the fovea were obtained for each eye. The presumed foveal center was determined as the area lacking the inner retinal layers in the macular region. If any disruption of any nature of the subfoveal ELM, EZ, and IZ was observed, the external retinal layer affected was classified as absent while a complete integrity was considered as present. The ONL thickness was measured manually on the most hyporreflective external layer at the central fovea. It was considered normal if its foveal thickness was 82.5 ± 11.1 μm [18] and abnormal if thinner. Two of the authors (KS and TF), who were unaware of the patients' clinical information, performed all of the measurements. When the two readers had different interpretations, a discussion was carried out to reach a conclusion and the senior author (MF) also gave his interpretation, if necessary.

Data was gathered in MO Excel and exported to IBM SPSS Statistics (v.24) for statistical analysis purposes. Visual acuity was converted to the logarithm of minimum angle of resolution (logMAR) units for statistical analyses [19]. Hand movement, light perception, and no light perception were classified as + 2, + 3 and + 4, respectively [20–22]; tables and figures were used to summarize data as appropriate. Observational agreement was evaluated by kappa test. Non-parametric data was applied due to a non-normal distribution, after Shapiro-Wilk's test ($p < 0.05$). Mean, median, and standard deviation were applied to continuous data. Spearman's correlation evaluated the independent association between BCVA and the considered retinal bands or individual features such as familiar affection, time from diagnosis, and pseudophakia. A multiple linear correlation was used to analyze the predictors of BCVA and the cumulative effect of previous considered factors. A p value of less than 0.05 was considered statistically significant.

Results

Forty-eight eyes of 24 patients were analyzed. Demographic characteristics are shown in Table 1. A moderate to very good agreement (value > 0.41) was found in all analyzed layers between both observers. For presentation purposes, only the left eye will be acknowledged. The BCVA in either eye of the patients was very similar with a strong and positive correlation between both eyes: $r_s(22) = .95$, $p < .001$*.

The correlation between BCVA was tested with the following variables: time from diagnosis, family history, pseudophakia, ELM, EZ, IZ status, and ONL. As the time from diagnosis increased, the BCVA decreased ($r_s(20) = 0.45$, $p = .04$*). A positive family history is correlated with worse BCVA ($r_s(19) = .44$, $p = .048$*). All OCT layers evaluated had a correlation with BCVA. The greater the ONL, the better the BCVA ($r_s(22) = -.63$, $p = .001$*). The presence of subfoveal ELM ($r_s(24) = -.78$, $p < .001$*), EZ ($r_s(22) = -.72$, $p < .001$*), and IZ ($r_s(22) = -.48$, $p = .02$*) was also correlated with better visual acuity (Fig. 1).

The number of layers affected was also associated with BCVA. There was a significant difference when three layers are affected versus no affected layers ($p = .003$) (Fig. 2). There was a strong positive correlation between the number of layers affected and a lower BCVA ($r_s(22) = .81$, $p < .001$). Figure 3 shows an SD-OCT example between a patient with low and higher BCVA and the difference between the affected layers.

Multivariate logistic regression with all variables analyzed was used to control for possible confounders. It was found that the studied variables contributed to 76%, adj $r^2 = .64$ ($F(6,12) = 6.31$, $p = .003$) of the BCVA variation. The single EZ presence leads to a BCVA change of − .37 (95% CI − 2.25 to − 0.198, $p = .02$*) logMAR. Likewise, the BCVA variation was not correlated with other of aforementioned variables (Table 2).

Table 1 Demographic characteristics of each patient regarding the OS

Background data	
Sex (male)	58.3% (*n* = 14)
Mean age (± SD)	52 (± 18.1)
Mean time from diagnosis	18.7 (± 17.7)
Positive family history	75% (*n* = 18)
Pseudophakia OS	50% (*n* = 12)
ELM absence	45.8% (*n* = 11)
EZ absence	79.2% (*n* = 19)
IZ absence	70.8% (*n* = 17)
Mean subfoveal ONL (μm)	31.6 (± 20.7)

ELM, external limiting membrane; *EZ*, ellipsoid band; *IZ*, interdigitation band; *ONL*, outer nuclear layer; *OS*, left eye; *SD*, standard deviation. These were classified as absent (−) or present (+)

Discussion

The aim of this study was to use SD-OCT to characterize changes in the outer retinal layers of RP patients and correlate them with visual acuity. As a first step to this goal, we aimed to identify with SD-OCT the layers of the outer retinal that are structurally affected in eyes with retinitis pigmentosa. The ONL is thinner than normal in most of our patients (23/24 eyes). Sandberg et al. associated the thinning of ONL to X-linked RP (XLRP) [23]. We did not perform genetic studies on our patients, but it is possible that this thinning of the ONL is present in most forms of RP. The EZ was discontinued in 79.2%, followed by IZ in 70.8% and finally ELM in 45.8% showing that all external retinal layers are affected by the disease. Higher visual acuities were correlated with a preserved structure of the outer retinal layers [8, 24–26]. As a bilateral disease, we found positive correlation between both eyes, in accordance with Matsuo et al. [8]. This was true both for visual function and for anatomic characteristics. As a genetic and progressive disease, time from diagnosis and a positive familiar affection is relevant for the visual function as patients with faster retinal degeneration probably having a diagnosis at an earlier age than patients with the slower variants of the disease. Both these variables correlated with a lower visual acuity, but this has been described extensively [5, 8, 27–31]. Pseudophakia is not correlated with visual acuity, which suggests that cataract surgery does not affect the natural history of the disease and the presence of an intraocular lens is not probably affecting progression of the disease and visual acuity. It is also known that cataract surgery improves visual acuity in RP patients with cataracts [17, 32].

The association between visual acuity and central retinal thickness was studied by Sandberg et al. and they concluded that both retinal thinning (due to cell loss) and retinal thickening (due to presumed edema) appear to be associated with lower visual acuity in patients with RP [9]. However, this could be misleading, as there may be patients with a normal retinal thickness that have had previous edema whose retina has not yet become atrophic and who may have a poor visual acuity. For all of these reasons, in our data, macular edema was an exclusion criterion.

As RP is mostly a disease of the outer retina, we focused our study in this area. The individual evaluation of the different SD-OCT layers of the outer retina (ONL, ELM, EZ, and IZ) brings new light into the subject. The univariate analysis showed a statistically significant correlation between a better visual acuity and the presence of each of the individual bands; however, only the EZ maintained statistical significance in a multivariate analysis. This is in agreement with other retinal diseases such as retinal detachment recovery after surgery [13, 33]. Furthermore, Liu et al. found a relationship between

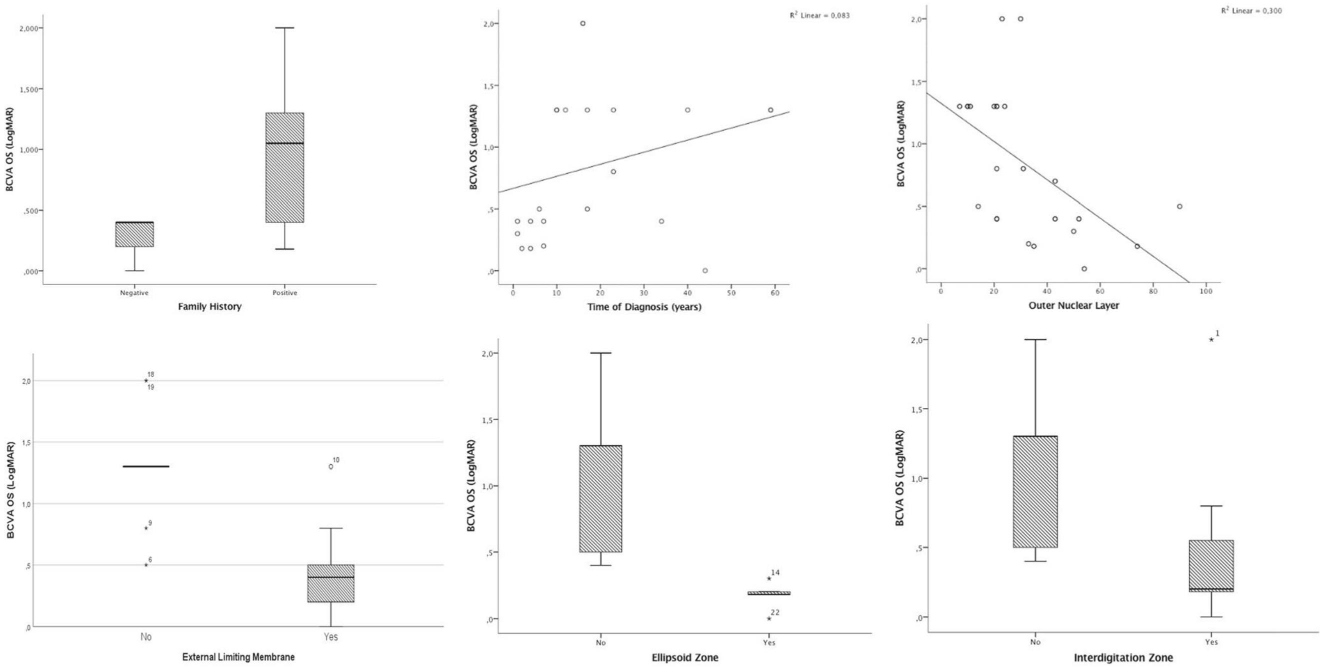

Fig. 1 Correlation between the BCVA of the left eye (OS) and studied variables (univariate analysis). *Top left*—family history: a positive family history is associated with an average worse BCVA. Boxplot shows the median and the quartiles of OS visual acuity regarding the family history. *Top middle*—time from diagnosis: there is an 8.3% correlation between the time from diagnosis and worsening of BCVA. *Top right*—outer nuclear layer: the thinner the outer nuclear layer, the worse the BCVA on a 30% correlation. *Below left*—external limiting membrane: boxplot that shows the BCVA and the presence or absence of external limiting membrane. Its presence is correlated with better visual acuity. *Below middle*—ellipsoid zone: boxplot that shows the BCVA and the presence or absence of ellipsoid zone. The presence of ellipsoid band is connected with better visual acuity. *Below right*—interdigitation band: boxplot that shows the BCVA and the presence or absence of interdigitation band. The presence of the interdigitation band is connected with better visual acuity

ganglion cell analysis, ELM, and EZ. The ganglion cells are thinner in patients with RP compared to those of controls, and the lesser length of ELM and EZ is correlated with worse visual acuity. The EZ length at the fovea demonstrated the strongest relationship with BCVA, which is accordant with our EZ results [27].

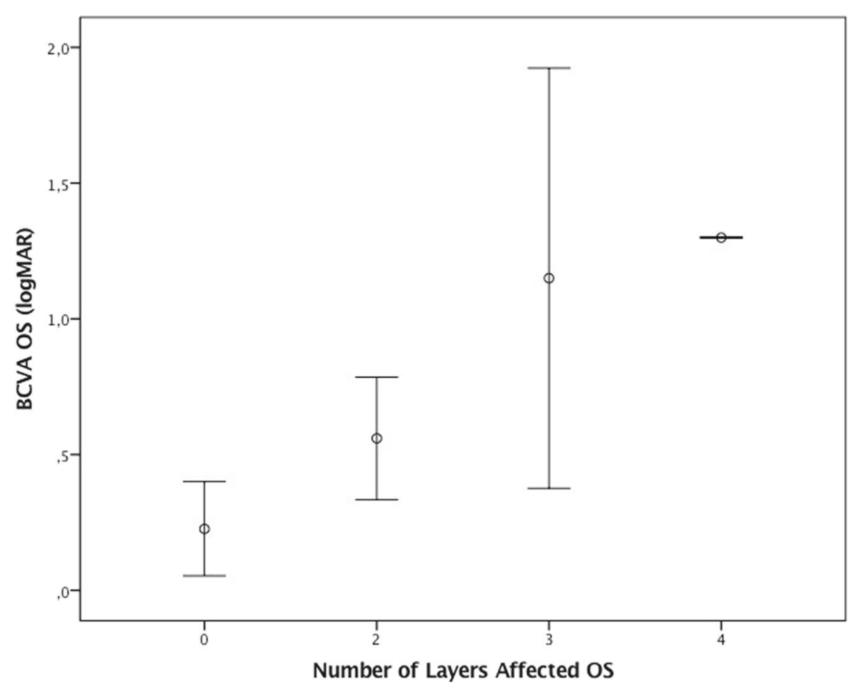

Fig. 2 Correlation between the number of OCT bands affected and BCVA. The more the layers affected, the worse the BCVA is, which is significant ($p = .003$) between 3 layers and no layers affected. Only one patient had all four layers affected

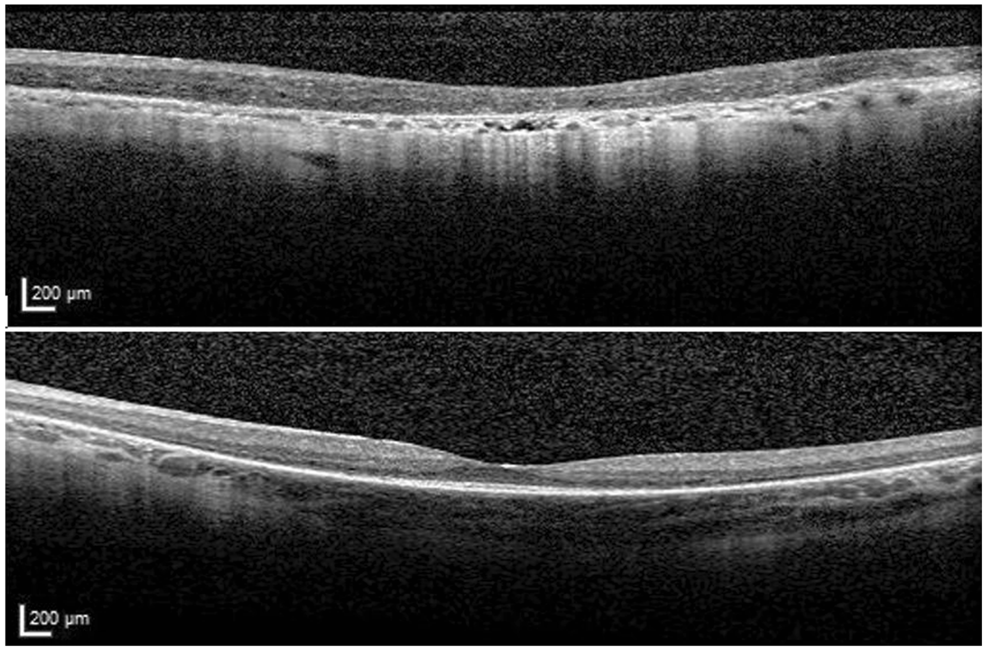

Fig. 3 *Top*—macular SD-OCT of a patient with a BCVA of + 1.3 logMAR. An example of an as absent ELM, EZ, and IZ. *Below*—macular SD-OCT of a patient with a BCVA of + 0.3 logMAR. The external retinal layers are well preserved in the foveal region. ELM, external limiting membrane; EZ, ellipsoid zone; IZ, interdigitation zone

Our study shows that the loss of layers of the outer retina interferes significantly with visual acuity. The more bands that are absent, the greater the visual acuity loss, demonstrating that there could be a cumulative effect. As the retinal layers are simultaneously disturbed, visual acuity is also worse. Matsuo et al. also found a correlation between the number of retinal layers affected and visual acuity. Nevertheless, they examined different retinal layers from the ones we evaluated. They evaluated the nerve fiber layer, the inner plexiform, and the outer plexiform layer, even though the paper is not clear on how the different layers were affected [8].

We also ran a multiple linear regression for studied variables to make a prediction for visual acuity. Time from diagnosis, family history, ONL, ELM, EZ, and IZ statistically significantly predicted BCVA which can be accounted by 64% in the studied variables. This is a large size effect, according to Cohen [34] which means that outer retinal layer affection is highly correlated with BCVA loss. The EZ is the only band that has an individual statistically significant result for this prediction in the multivariate analysis. Pathological studies about RP confirmed the EZ as the earliest histopathological change in the outer segments of photoreceptors, where the EZ is located, due to outer segment shortening, cytoplasmic densification, axonal elongation, and, ultimately, cone cell death [11, 13, 35]. We also concluded that 79.2% of patients had an absent EZ, 70.8% had an absent IZ, 45.8% had an absent ELM, and 95.8% had a thin ONL. In RP, photoreceptor outer segment loss is followed by loss of the inner segments and cell body—this seems to be in agreement with our results. However, the ONL comprises rod and cone nuclei and in RP, the rods degenerate earlier than cones [26, 36]. Robson et al. also demonstrated that a ring of high-density autofluorescence (AF) was correlated with a more severe scotopic sensitivity loss even with a preserved photopic sensitivity. This suggests that a mild macular photoreceptor dysfunction may precede significant accumulation of lipofuscin and increased AF, even with intact but dysfunctional rods in RP patients [37].

Table 2 Coefficients of all variables included in multivariate linear regression to predict to BCVA

	Unstandardized coefficients *B* (std. error)	Standardized coefficients Beta	*t*	Sign	95% confidence interval for *B*
(Constant)	.86 (.43)		2.01	.07	− .07 to 1.79
ONL	.00 (0.1)	− .003	− .01	.99	− .02 to .02
ELM	− .51 (.30)	− .42	− 1.7	.12	− 1.17 to .15
EZ	− 1.23 (.47)	− .83	− 2.6	.02*	− 2.25 to − .20
IZ	.75 (.41)	.55	1.85	.09	− .14 to 1.64
Family history	.35 (.29)	.21	1.22	.25	− .28 to .97
Time from diagnosis	.003 (.006)	.08	.49	.64	− .1 to .02

ONL, outer nuclear layer; *ELM*, external limiting membrane; *EZ*, ellipsoid band; *IZ*, interdigitation band; *statistically significant. The ellipsoid band was the only factor that had statistical significance in predicting visual acuity in the multivariate model which predicts visual acuity in RP patients

In our study, all outer retinal bands were evaluated and show how each layer may contribute to visual acuity in RP. However, we are aware that the cross-sectional design is a limitation of our study. A prospective study in the early stages of the disease may help to understand its pathogenesis by confirming the order in which the outer retinal layers are affected. Unfortunately, the cross-sectional design of the study and the advance disease state do not allow us to draw all the conclusions.

Understanding the order and speed in which outer retinal changes occur in RP may lead to a better understanding of the disease and its different phenotypes. This could be helpful for patient counseling and prognosis without the burdens of genetic testing.

Limitations of our study include the small sample size and the cross-sectional design. Our study only evaluated the fovea, which is also a limitation. RP is characterized by rod degeneration before cone degeneration. It will be important in the future to evaluate SD-OCT changes in the more peripheral retinal and correlate them with other aspects of visual function. RP is a disease which comprises multiple genes and it would be important to include genetic tests in the future to turn these results more comprehensive. Unfortunately, we were not able to perform genetic analysis as genetic testing is still not possible in many everyday clinical practices especially outside of research protocols.

A larger prospective study is important to reproduce results and possibly identify how the different retinal layers are affected by the disease and eventually identify significant predictors of prognosis for different phenotypes of RP.

In conclusion, our data confirms the influence of the integrity of the outer retinal layers on the decrease of BCVA. The ellipsoid band seems to be the most important layer in predicting visual acuity, but the outer nuclear layer, external limiting membrane, and interdigitation zone may have a cumulative weight in the natural history of this disease.

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Compliance with ethical standards

All procedures were in accordance with the ethical standards of the institutional, document number 132/2017, and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All data were performed based on anonymized data and none of the presented results can identify any patient.

Conflict of interest The authors declare that they have no conflict of interest.

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