The Transition Zone between Healthy and Diseased Retina in Patients with Retinitis Pigmentosa

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PURPOSE. To describe the structural changes in the transition zone from relatively healthy retinal regions to severely affected regions in patients with retinitis pigmentosa (RP) using frequency domain optical coherence tomography (fdOCT).

METHODS. FdOCT line scans of the horizontal meridian were obtained from one eye of 13 patients with RP and 30 control subjects. The patients had normal or near normal foveal sensitivities and visual field diameters $\geq 10^\circ$. Using a computer-aided manual segmentation procedure, the locations at which the outer segment (OS) and outer nuclear layer plus outer plexiform layer (ONL+) thicknesses fell below the 95% confidence interval of the controls were measured, as were the locations at which the OS layer disappeared and the locations at which the ONL+ was reduced to an asymptotically small thickness.

RESULTS. The progression from healthy to severely affected regions followed a common pattern in most patients. Region A, the central region including the foveal center, had normal OS and ONL+ thickness. Region B had abnormal OS but normal ONL+ thickness. Region C had abnormal but measurable OS and ONL+ thicknesses. In Region D, the OS layer disappeared, as did the IS/OS line, and the ONL+ thickness decreased further. In Region E, the ONL+ reached an asymptotic thickness.

CONCLUSIONS. The structural changes in the transition zone followed an orderly progression from a thinning of the OS layer, to a thinning of the ONL+, to a loss of the OS layer, to an ONL+ reduced to an asymptotically small level. (*Invest Ophthalmol Vis Sci.* 2011;52:101–108) DOI:10.1167/iovs.10-5799

Retinitis pigmentosa (RP), a group of hereditary diseases, primarily affects the photoreceptor/pigment epithelial complex. Typically visual loss starts in the peripheral retina and progresses toward the fovea. Relatively early in the disease process the sensitivity of the central retina, including the fovea, can be normal or near-normal, while the sensitivity of the peripheral retina might be severely decreased or nonmeasurable. The transition zone from a relatively healthy central

region to a severely affected peripheral retina can now be studied in vivo with optical coherence tomography (OCT).

Recently, Jacobson et al.¹ characterized this transition zone in patients with Usher Syndrome 1B (USH1B), an autosomal recessive syndromic form of RP, caused by MYO7A mutations. Their purpose was to identify the optimal location for injections for gene replacement. To this end, they developed a qualitative framework that described the changes in the transition zone in terms of regions with different morphologic characteristics. Some of the key features of this framework appear to fit the transition zones in patients with other non-syndromic forms of RP.^{2,3}

An understanding of the transition zone has importance beyond the implications for therapeutic approaches. First, because RP progresses from the midperiphery to the foveal center, it is plausible that the transition zone at any moment in time is a model for the changes taking place at any retinal location over time. That is, the Jacobson et al.¹ framework is also a potential description of disease progression. In addition, it is possible that a detailed quantitative description of the transition zone may help in differentiating among hereditary degenerative retinal diseases and/or genetic mutations of these diseases.

Given the potential importance of the transition zone, we extended the work of Jacobson et al.¹ First, we took an operational approach to defining regions of the transition zone. In particular, we determined the locations at which the thickness of different layers of the outer retina fell below normal limits. Second, while Jacobson et al. measured the outer nuclear layer (ONL), they did not measure directly the outer segment (OS) layer, presumably because this layer was difficult to delineate with the automated algorithm they used. With frequency domain (fd) OCT, it is possible to differentiate an OS layer. In fact, using fdOCT, we have recently measured the thickness of the OS+retinal pigment epithelium (RPE) layer in patients with RP.^{4,5} Taking the OS layer into consideration could have an impact on a model of the transition zone. For example, the Jacobson et al. framework starts with a normal ONL thickness, presumably a sign of a region with normal sensitivity.^{1,6,7} Although this may be generally true, we^{4,5} observed regions over which the ONL was of normal thickness, but the OS was thinner than normal.

Here we test a simple hypothesis. In particular, because RP is a defect of the receptor/RPE complex, we assume that structural damage (thinning) should be seen first in the outer segment region, and then at the ONL, and we hypothesize that the transition zone should show the same pattern.

METHODS

Subjects

The study included 13 RP patients (27.8 ± 17.0 yrs, range: 11 to 59 years) and 30 controls (35.7 ± 14.0 yrs, range: 11 to 65 years). Patients

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were diagnosed with RP based on the appearance of the fundus, clinical history, visual fields, and full-field electroretinogram results. The genetic types of these patients were as follows: x-linked, 8; isolate, 4; dominant, 1. Three of the x-linked patients had the RPGR gene mutations. The 13 patients were selected from a larger sample of patients on the basis of visual field characteristics as tested with a 30-2 program (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA). To be included, a patient's visual field had to have a normal or near normal foveal sensitivity (≥ 32 dB) and a diameter $\geq 10^\circ$. These patients had best visual acuities between 20/15 and 20/50 with 9 better or equal to 20/25. Patients were excluded if they had a refractive error greater than ± 6.0 diopters spherical or ± 2.0 diopters cylindrical, evidence of macular cysts (or other macular pathologies such as epiretinal membranes), a history of other ocular diseases (e.g., glaucoma), or OCT scans of poor quality. Twenty of the 30 controls and all 13 RP patients were also included in an earlier study.⁴

All subjects were tested at the Retina Foundation of the Southwest. The tenets of the Declaration of Helsinki were followed, and all subjects gave written informed consent after a full explanation of the procedures was provided. Consent procedures were approved by the Institutional Review Board of UT Southwestern Medical Center.

Frequency-Domain OCT

All individuals were scanned (Spectralis HRA+OCT; Heidelberg Engineering, Vista, CA) using the eye-tracking feature (ART). A 9-mm line scan along the horizontal meridian, and centered on the fovea, was obtained as an average of 100 scans (see Fig. 1A). The scan from one eye of each individual was analyzed. When scans of both eyes were available, the better OCT image was selected. If both scans were of comparable quality, the eye with higher visual acuity was chosen; if visual acuity was the same in each eye, the eye with lower correction was chosen.

Segmentation Procedure

Eight borders, labeled 1 through 8 in Figure 1B, were segmented using a manual segmentation procedure (MATLAB, v7.4; Mathworks, Natick, MA).⁴ The segmented borders were the following: vitreous/RNFL: the inner limiting membrane (i.e., the border between the vitreous and the retinal nerve fiber layer [RNFL]); RNFL/RGC: the border between the RNFL and the retinal ganglion cell (RGC) layer; IPL/INL: the border between the inner plexiform layer (IPL) and the inner nuclear layer (INL); INL/OPL: the border between the INL and the outer plexiform layer (OPL); OLM: outer limiting membrane; IS/OS: the border between the inner segment (IS) and outer segment (OS) of the receptors; OS/RPE: border between OS and RPE; BM/choroid: the border between Bruch's mem-

brane (BM) and the choroid. To ensure that the degree of curvature of the line scan did not impact thickness results, the line scans were flattened in our software program before the thickness of the retinal layers was calculated, although the unflattened results were very similar. Flattening the scans caused the uneven appearance of the curves in Figures 2D and 2E.

Using the locations of these 8 boundaries, we defined 6 retinal layers as shown in Figure 1B:

- RNFL : the distance between 1 (vitreous/RNFL) and 2 (RNFL/RGC);
- RGC+IPL : the distance between 2 (RNFL/RGC) and 3 (IPL/INL);
- INL : the distance between 3 (IPL/INL) and 4 (INL/OPL);
- ONL+ : the distance between 4 (INL/OPL) and 5 (OLM);
- OS : the distance between 6 (IS/OS) and 7 (OS/RPE);
- RPE : the distance between 7 (OS/RPE) and 8 (BM/choroid).

Technical aspects should be addressed. First, outside the central fovea, what we call the OS layer contains a mix of rod and cone outer segments. It also contains processes from the RPE cells that surround these outer segments. Second, care must be taken in interpreting what is called the ONL and OPL in OCT scans (Fig. 1). There are two histologic definitions of the OPL in the literature. Cajal⁸ defined the OPL as the region of synaptic connections between the receptors and the cells of the INL. On the other hand, Polyak⁹ defined it as this region plus the fibers of Henle, that is, the "axons" from the receptors. Here we will use Cajal's definition, the region of synapse, because it appears to be the one most often used in OCT work.¹⁰ However, whatever one calls the actual synaptic region, it is a relatively narrow region, unlike the IPL, which has multiple layers of synaptic connections. We did not attempt to measure the thickness of the OPL because in addition to being narrow, it is easily confused with the receptor fibers of Henle. For example, if we compare the temporal and nasal sides of the fovea in Figure 1B, the blurred/fuzzy region of darker gray (red arrow) on the temporal side cannot be Cajal's OPL. This local "thickening of the OPL" can be seen in scans from machines from different manufacturers. Although it is not certain what causes this local phenomenon, it is probably due to the fibers of Henle (i.e., axons from cone receptors), which are technically part of Cajal's ONL. These fibers may be more or less visible depending on the angle of incident light.¹¹ In any case, we refer to the ONL+OPL in Figure 1B as ONL+ and measure it from the OLM to the proximal edge of the OPL as shown by the light blue vertical line. In other words, what we are calling the ONL+ contains the receptor cell bodies, receptor fibers (including the fibers of Henle),

FIGURE 1. (A) A fdOCT 8.6 mm scan of the horizontal meridian of a normal retina. (B) Same scan as in (A), but with the borders segmented shown as the colored lines.

FIGURE 2. (A) fdOCT scan of the horizontal meridian of a patient with RP. Colored lines indicate the borders segmented. (B) Magnified version of the central portion of the scan in (A). Red arrows indicate the point at which the OLM is no longer apparent. (C) Same as in (B) but with segmented lines. (D) OS thickness profiles across retina for the scan in (A) (blue) and for the mean (bold black) and ± 2 SD (thin black) of scans from 30 healthy controls. The filled purple symbols mark the points at which the OS thickness falls below the 95% CI (black lines), and the green symbols mark the points at which the OS thickness approaches zero. (E) ONL+ thickness profiles across retina for the scan in (A) (light blue) and for the mean (bold black) and ± 2 SD (thin black) of scans from 30 healthy controls. The filled red symbols mark the points at which the ONL+ thickness falls below the 95% CI (black lines), and the blue symbols mark the points at which the ONL+ thickness approaches an asymptotic level.

and OPL connection to cells of the INL. Note also that the ratio of axons to cell bodies varies with eccentricity. The axonal contribution is small in the central fovea, increases to more than one-half the ONL thickness in the parafovea, and then decreases again in the peripheral retina.^{9,12}

RESULTS

Transitions to Abnormal Thickness in the Outer Segment and Outer Nuclear Layers

Our primary focus here is the receptor region. Figure 2A is the horizontal scan of one of the patients with the central portion expanded in Figures 2B and 2C. The blue curves in Figures 2D and 2E show the thickness of the OS layer and ONL+ as a function of distance from the center of the fovea. The black curves in these panels are the mean (bold) and 95% confidence intervals (CI) (thin) for the group of 30 controls. As shown by the purple circles in Figure 2D, we marked the nasal and temporal points at which the patient's OS thickness fell below

the CI, that is, below the mean minus 2 standard deviations of the controls. Figure 2E shows a similar analysis for the ONL+, where the red circles mark the point at which the thickness falls below the CI.

Eight of the 13 patients had a foveal region in which the OS thickness was within the CI, although this region was ≤ 100 μm in two cases. We call this central portion of the retina region A. Region A has an OS thickness within the normal CI.

In all 13 patients, the ONL+ was within normal limits in the center of the field, including in region A. However, there was typically a region, beyond region A, with an abnormal OS thickness, but with an ONL+ thickness within the normal CI. We call this region B. Operationally, region B was defined as the portion of the scan between the purple (OS below CI) and red (ONL+ below CI) symbols in Figures 2D and 2E. The red bars at the bottom of Figure 2E show the extent of this region for this patient. For the nasal retina, there was a measurable region B in 11 patients; in one patient it was not present (i.e., the purple and red symbols coincided); and in one patient the

OS region, as well as the other layers, was normal to the end of the scan. For the temporal retina, there was a measurable region B in 10 patients, in two patients it was not present (purple and red symbols coincided), and in one patient the OS region was normal to the end of the scan. The median extent of region B was 460 μm (nasal) and 530 μm (temporal), with ranges of 0 to 1410 μm (nasal) and 0 to 2240 μm (temporal).

Transitions to Asymptotic Thickness in the Outer Segment and Outer Nuclear Layers

Two other transition points were identified in the OS and ONL+ thickness profiles. First, for the OS layer (Fig. 2D), we marked the point, green square, at which the OS thickness fell to 0, that is, the IS/OS line (dark blue in Fig. 2C) approached the OS/RPE border (purple) and disappeared. This point nearly always occurred at a more eccentric location than did the end of region B, the end of the normal ONL thickness: that is, there was typically a region where both the OS and ONL+ were present, but abnormal in thickness. We call this region C; its extent in Figure 2E is shown as the green bars at the bottom of the figure. A measurable region C was present in all but 3 of the 24 hemifields with abnormal OS regions. The median extent of region C in these 24 hemifields was 700 μm (nasal) and 640 μm (temporal), with ranges of 120 to 2120 μm (nasal) and 270 to 2650 μm (temporal).

Beyond the point at which the OS layer disappeared, there was also typically a region over which the ONL+ continued to decrease until it asymptoted at a thickness of approximately 25 to 30 μm (dotted light blue line in Fig. 2E). The point at which this asymptotic thickness was reached was approximated as shown in Figure 2E by the blue squares. To aid in estimating these points, a horizontal line was drawn through the more peripheral points as shown by the dotted blue line in Figure 2E. In all but two of the 24 hemifields (same patient), this point occurred at a more eccentric location than did the end of the OS layer. Thus, there was typically a region D where the OS layer was missing on the OCT scan, but the ONL+ layer had not yet reached an asymptotic thickness. The blue bar at the bottom of Figure 2E indicates the extent of this region. The median extent of region D in these 22 hemifields was 965 μm (nasal) and 690 μm (temporal), with ranges of 0 to 1800 μm (nasal) and 170 to 2980 μm (temporal).

Finally, we defined region E, as the region over which the OS layer was not present and the ONL+ had reached an asymptote. Of the 24 hemifields with abnormal OS regions, 23 showed a region E, and this region extended to the end of the scan.

The Outer Limiting Membrane and the Inner Segment

A measure of receptor IS thickness could have been obtained as well by taking the difference between the OLM and the IS/OS borders. Instead, we marked the position at which the OLM disappeared (i.e., there was no longer a measurable IS thickness). The termination of the OLM could be identified in 22 hemifields. In three hemifields the OLM extended to the end of scan, and in one scan it was difficult to segment. In all 22 cases, the OLM terminated after the OS layer terminated (IS/OS border disappeared). The termination of the OLM in Figure 2B is shown by the red arrows.

Regions of the Transition Zone

Table 1 summarizes our working framework for categorizing the pattern of outer retinal loss across the transition zone from healthy to affected retina. Figure 3 is a summary of the thickness of the OS layer (panels A and B) and ONL+ (panels C and D) for each patient (different color symbols) analyzed sepa-

TABLE 1. Changes Seen in Outer Retina across Transition Zone

Region	Characteristics of OS Layer and ONL+
A	OS and ONL+ thickness within normal CI
B	ONL+ within CI and OS thickness below CI
C	OS and ONL+ below CI, but present
D	No OS (or IS/OS line); ONL+ abnormal and still decreasing
E	No OS and asymptotic ONL+

rately for the nasal (left column) and temporal (right panel) halves of the scans. Each point in Figure 3 is the patient's average thickness expressed relative to the thickness of the controls averaged over the same portion of the retina. Consider the OS region first (panels A and B). As expected, the OS thickness is near, but typically below, the mean normal value (1.0) in region A and then falls to 0 in region D. The ONL+ (panels C and D) starts near the control values and falls to a smaller (asymptotic) value in region E. Recall by definition, the OS thickness is within the normal CI in region A, while the ONL+ is within the normal CI in regions A and B. The points, however, fall below the mean normal value of 1.0 because we define the end of these regions based on when the thickness falls outside the CI, not when it falls below the mean of the normal values.

Because the width of any given region differs across hemifields, it is not possible to relate the data in Figure 3 to confidence intervals based on our controls. The same data are shown in Figures 4A–D as *z*-scores (i.e., the number of standard deviations above or below the mean of the controls). To obtain these *z*-scores, the thickness of each region of each hemifield was related to the distribution of the 30 control thicknesses for the same region width. The black diamonds show the average ± 1 SE for the patients. As expected, in region A nearly all the points fall above -2 SD (lower dotted line) for both the OS and ONL+ layers. Likewise, for region B, nearly all the points for the ONL+ layer (Figs. 4C, 4D) fall above this limit, while all the points for the OS layer (Figs. 4A, 4B) fall below. Thus, Figures 3 and 4 supply quantitative validation of our framework in Table 1. Although our framework is not meant to be a quantitative model, from Figure 3 it appears that OS length decreases by 40% before ONL+ thickness is affected (region B) and that an 80% reduction in OS is associated with only about a 25% decrease in ONL+ (region C).

Post-Receptor Layers

Although our primary purpose was to categorize the outer layers of the retina, we also measured the thickness of the inner retinal layers. Figure 5 shows the *z*-score presentation, as in Figure 4, for the INL, RGC+IPL layer, and RNFL. In Figures 5A and 5B, the INL thickness is, on average, close to the mean of the controls, although on the nasal side, over 80% of the points in Figure 5A are thinner than the controls, i.e., fall below the dashed line. On the temporal side, the INL layer is thicker than the controls for three hemifields in two to four of the regions. However, there does not appear to be any evidence for a region-specific change in the INL. On the other hand, for some hemifields the RGC+IPL thickness in the temporal retina and the RNFL thickness in the nasal retina are thicker than normal in regions D and E, consistent with our previous findings.⁴ Note that the RNFL of the temporal retina is not shown because it is the horizontal raphe region and thus very thin in controls.

DISCUSSION

Patients with hereditary degenerative diseases of the photoreceptors such as RP can exhibit a normal or near-normal foveal

FIGURE 3. (A) Symbols are the patients' OS layer thickness in the nasal retina normalized by dividing by the mean thickness for the 30 controls over the same portion of the retina. (B) Same as in (A), but for the temporal retina. (C) Same as in (A), but for the ONL+ thickness. (D) Same as in (B), but for the ONL+ thickness.

sensitivity combined with severe visual loss in the periphery. The nature of the transition zone between the central fovea and the more peripheral regions with severe field loss has important implications for therapeutic strategies,¹ as well as for an understanding of the nature of disease progression. Our purpose here was to characterize the changes in the layers of the retina, especially the receptor layers, in the transition zone of patients with RP. We build on previous work¹ by adding a measure of the OS thickness and by providing operational/quantitative definitions of the characteristics of the transition zone. In particular, we measured the location at which the thickness of the OS and ONL+ layers fell below normal limits, as well as the locations at which the OS thickness appeared to approach zero, the OLM could no longer be detected, and the ONL+ was reduced to an asymptotically thin value. Although the details of the pattern of loss in the transition zone varied across patients, the consistency of the general pattern of change across our 13 patients was striking.

Working Framework/Qualitative Model

Table 1 contains our working framework or qualitative model identifying five regions, and Figures 3 and 4 supply the sup-

porting quantitative data. These regions are artificial divisions of a continuous change from healthy to severely affected retina. In any case, by defining these regions in terms of quantitative changes in the receptor region, it became clear that there was an orderly and understandable progression across the transition zone. That is, although a region could be missing in a particular hemifield, it was nearly always the case that the order from A through E was maintained.

The progression of changes implied by this ordering is consistent with a disease process that begins in the OS. In particular, phrased as a progressive process, the results are consistent with the following hypothetical continuum of structural changes: healthy retina (A: OS and ONL thickness within normal limits), OS affected (B: thinner OS layer), ONL affected (C: thinner ONL layer), extensive or complete loss of OS (D: IS/OS disappears), extensive or complete loss of IS layer (OLM disappears), and extensive or complete loss of cell bodies in ONL (E: asymptotic thickness of ONL+). To this we should probably add a region F where there is a disruption of the RPE region. We did not focus on the RPE as, by and large, the RPE region was of normal appearance and thickness in all 13 patients, even in region E. The exceptions to this were minor as

FIGURE 4. (A) Symbols are the patients' OS layer thickness in the nasal retina expressed as z -scores. The difference between a patient's OS thickness and the mean thickness for the 30 controls, over the same portion of the retina, was divided by the SD of the 30 control values. (B) Same as in (A), but for the temporal retina. (C) Same as in (A), but for the ONL+ thickness. (D) Same as in (B), but for the ONL+ thickness.

illustrated by the local disruption of the RPE in Figure 2A (violet arrow). However, in patients with RP, more severely affected than those in this study, we have observed a thinning and disruption of the RPE layer as reported by others (e.g., Refs. 2, 13, 14).

Comparison to Transition Zone in Patients with USH1B

Jacobson et al.¹ partitioned the transition zone of the USH1B-MYO7A retina based on changes in thickness of the ONL, OPL, and INL, as well as the visibility of the OLM. Our results agree with their major finding. That is, both studies report a consistent pattern across patients, including a progressive thinning of the ONL from normal to abnormal with distance from the foveal center. However, by measuring OS thickness, we divided the region of normal ONL thickness into two regions, one with normal OS thickness and one with abnormal OS thickness. Based on our earlier work,⁴ we know that sensitivity can be abnormal in the region with normal ONL, but abnormal OS, thickness. Thus, although a normal OS thickness may imply a normal sensitivity, a normal ONL thickness does not.

On the other hand, there are minor differences between our findings and theirs. For example, they observed a greater prominence of the OLM in their region A, a region with an otherwise approximately normal retina. In general, this was not apparent in the scans we analyzed. However, probably the biggest difference between our framework and theirs concerns the thickness of the INL. In their framework, as the retina progressed from normal (their region A) to severe field loss, the INL thickened to a level above normal limits, while the ONL decreased to the point where it was no longer detectable.¹ In our study, in general the INL had approximately normal thickness throughout the transition from normal to severely affected retina. Even in the three patients who showed an apparent thickening of the INL in the temporal retina, this thickening was not region specific (Fig. 5B). On the other hand, it is clear that an INL thickening can occur in both humans (cf. Figs. 5 and 6B in Aleman et al.)² and animals (cf. Fig. 7 in Aleman et al.).² Thus, we must ask why is it not more common in our results. There are at least three possible reasons. First, although we take the Jacobson et al.¹ framework as our starting point, in fairness they make no claims about the frequencies of their

FIGURE 5. Same as in Figure 4 but for INL (A, B), RGC+IPL layer (C, D), and RNFL (E).

different regions, including the thickening of the INL layer, across patients. Second, most of the INL thickening they have reported occurred beyond 4 mm from the foveal center, while our transition zones are within 3 mm. Thus, our framework

needs testing in patients with transition zones beyond the central 3 mm, where the INL thickening may be more common. Finally, as they^{1,2,15} point out, a thickening of the hyporeflective layer identified as the INL may represent intermin-

FIGURE 6. (A) A peripheral portion of the scan in Figure 1B. (B) A similar portion of the retina for the scan in Figure 2A. (C) Same scan as in (B), but magnified and without the borders. The green arrow shows the end of a discernible INL/OPL border.

gled INL and residual ONL nuclei, as can be seen in the animal model work of this group.² In particular, we defined the INL as the thickness between border 3 (IPL/INL) and border 4 (INL/OPL). This is illustrated in Figure 6A, which shows a peripheral portion of the normal scan from Figure 1B. A similar portion of the scan from the patient in Figure 2 is shown in Figure 6B and again in Figure 6C, but expanded and without segmentation lines in this case. When the INL/OPL is no longer discernable, as shown by the dark green arrows in Figures 6B and 6C, we do not measure a thickness for the INL. That is, because we define the INL as the difference between borders 3 and 4, if border 4 is missing, as in Figure 6B, then we do not report an INL thickness. On the other hand, the Jacobson et al.¹ framework defines the INL and ONL as the two hyporeflexive regions between the RPE and vitreal borders. Thus, when the border between them is no longer present, then the single layer would be considered the INL. We find that, in the more affected regions, the INL/OPL⁴ and the IS/OS⁶ borders, as well as the OLM,⁵ become indistinct. Because the entire region between our border 7 (OS/RPE) and our border 3 (IPL/INL) can appear hyporeflexive, by the Jacobson et al. definition this is a thick INL, although as mentioned above they point out that this could also be an intermingling of INL with residual ONL. Thus, it remains an open question as to the conditions under which the INL is normal versus when it is thicker due to a remodeling.

A related, but different, issue concerns the reports^{2,3,16} of an increased thickness of the combined inner retina (i.e., INL, IPL, RGC, RNFL). As indicated in Figure 5 and previously reported,⁴ for horizontal midline scans, we believe that most of the thickening in the nasal retina is due to a thickening in the RNFL. In the temporal retina, the thickening, if present, is modest and in the RGC+IPL layer in only some patients.

CONCLUSIONS

The patients with RP studied here show a consistent pattern of change across the transition zone from a reasonably healthy foveal center to regions that are severely affected. This pattern starts with a thinning of the receptor OS layer, is followed by changes in the ONL, progresses to asymptotic losses of the OS and ONL+ layers, and, finally, advances to a disruption of the RPE and what remains of the ONL+. It will be of interest to see if this pattern is different in different RP mutations and/or in different diseases of the receptors.

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