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Distribution of cystoid spaces in RP

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1 Abstract

2 PURPOSE: To investigate the prevalence and spatial distribution of cystoid spaces (CS)  
3 in retinitis pigmentosa (RP) patients with spectral domain optical coherence tomography  
4 (SD-OCT).

5 METHODS: 529 eyes of 275 patients with RP were examined with spectral domain  
6 optical coherence tomography. Presence or absence of CS was judged for each eye.  
7 Retinal layer and outer retinal status where the CS existed were also investigated.  
8 Statistical analysis was done using one eye per one patient.

9 RESULTS: CS were present in 119/529 eyes (22.5%) of 74/275 patients (26.9%). There  
10 were no significant differences between the cases with and without CS except for central  
11 foveal thickness ( $p < 0.001$ ). CS were noted in inner nuclear layer (INL) in almost all eyes  
12 (98.6%) and outer nuclear layer (ONL)/outer plexiform layer (OPL) was also involved in  
13 many eyes (27.8%). CS were sometimes seen in ganglion cell layer (6.9%). CS were  
14 predominantly (78.9%) distributed in the relatively preserved retina where external  
15 limiting membrane was retained. The presence of epiretinal membrane (ERM) or  
16 posterior vitreous adhesion was associated with the presence of CS ( $p < 0.001$ ) but  
17 showed no relationship with the spatial location of CS ( $p = 1.000$ ).

18 CONCLUSIONS: The prevalence of CS in RP patients was 26.9% and contrary to  
19 previous reports, most CS were present in INL. In addition, most CS were observed in  
20 relatively retained retina, which is compatible to prevailing notion. ERM or posterior  
21 vitreous adhesion was also associated with the development of CS. The distribution of

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1 CS in inner and preserved retina may provide insight for the pathogenesis of CS in RP.

2

## 1 INTRODUCTION

2 Retinitis pigmentosa (RP) is sometimes complicated by cystoid macular edema (CME),  
3 which may impair central vision in any stage of the disease.<sup>1</sup> Several therapeutic  
4 strategies have target CME in RP patients including topical or oral administration of  
5 carbonic anhydrase inhibitor,<sup>2-7</sup> steroid administration,<sup>8-10</sup> intravitreal injection of  
6 anti-vascular endothelial growth factor agent,<sup>11</sup> photocoagulation,<sup>12, 13</sup> or even  
7 vitrectomy.<sup>14</sup> The beneficial effects of each of these therapies are not consistently  
8 observed in all patients. The establishment of therapeutic approaches is complicated by  
9 the limited knowledge regarding the pathophysiology of CME in RP patients. Some  
10 mechanisms including anti-retinal antibodies<sup>15, 16</sup> vitreous traction,<sup>12</sup> RPE dysfunction,<sup>17,</sup>  
11 <sup>18</sup> and Müller cell edema<sup>19-21</sup> were proposed. If there are several etiologies for the  
12 development of CME, different therapeutic strategies may be required to treat each  
13 etiology. However, the evidence for how these mechanisms are involved in the  
14 development of CME is limited.

15 To investigate the etiology of CME in RP patients, we focused on retinal layers  
16 where cystoid spaces (CS) are located. As cysts are not limited to macular tissues, we  
17 use the term cystoid spaces in the present study. Some of the retinal structures, e.g., the  
18 inner and outer plexiform layers contain abundant tortuous dendritic processes,  
19 connecting fibers, and invaginated synapses, which are considered to work as a  
20 barrier.<sup>22</sup> The external limiting membrane consists of zonula adherens between apical  
21 processes of Müller cells and photoreceptors of the inner segment, and limits the

1 diffusion of large molecules such as albumin.<sup>23</sup> The semi-permeable nature is thought to  
2 contribute to the accumulation of intra-retinal fluid.<sup>24</sup> Thus, we hypothesize that these  
3 structures may affect the distribution of CS in different etiologies.

4         The main location of CS in pseudophakic macular edema is the inner nuclear  
5 layer (INL), throughout the majority of retinal layers in patients with central retinal vein  
6 occlusion, and predominantly in the outer plexiform layer (OPL) in diabetic macular  
7 edema.<sup>25</sup> In addition, Tsujikawa *et al.* investigated retinal vein occlusion and suggested  
8 that CME progresses to serous detachment when the barriers of external limiting  
9 membrane (ELM) break down.<sup>26</sup> These studies indicate that the distribution of CS is  
10 dependent on the etiology and retinal status and the patient. While histological  
11 examination of the retina is both difficult and impractical in routine clinical investigations,  
12 optical coherence tomography (OCT) is widely used to study retinal pathologies and has  
13 also been used for the diagnosis and monitoring of RP. For example, OCT has been  
14 shown to be more sensitive, or at least as sensitive, as fluorescein angiography for the  
15 detection of CME in RP.<sup>27-29</sup> Other studies showed that evaluating retinal structure with  
16 OCT is useful for the assessment of retinal function.<sup>30-36</sup>

17         Little evidence exists as to which layer is predominantly involved in the  
18 development of CS associated with RP, with the exception of a single report with a small  
19 case series.<sup>37</sup> We assumed that detailed evaluation of retina using OCT in larger  
20 numbers of RP patients would provide some insight in the pathogenesis of CME in RP.

21         In addition to the retinal “layers”, we investigated retinal “areas” where CS exist.

1 There is a prevailing notion that CME less frequently occurs in the late stages of the  
2 degenerative pathology,<sup>1</sup> but this is yet to be clearly shown to our knowledge. In the  
3 present study, we also investigated outer retinal integrity and the association with CS  
4 location to confirm whether CS preferentially occurs in early to moderate stage RP. As an  
5 indicator of outer retinal preservation, ELM, which were reported to be correlated with  
6 visual function in various diseases<sup>38, 39</sup> was used.

## 7 **METHODS**

8 All procedures conformed to the tenets of the Declaration of Helsinki and the study  
9 design was prospectively approved by the Institutional Review Board and ethical  
10 committee at Kyoto University Graduate School of Medicine. The review board waived  
11 the need for written informed consent because the study design consisted of  
12 retrospective chart review.

### 13 **Participant information**

14 Diagnosis of RP was made with clinical interview of family history, the presence of night  
15 blindness, characteristic fundus appearance, concentric or ring shaped scotoma in  
16 Goldmann perimetry, and the result of electroretinogram (ERG). Full-field ERGs were  
17 recorded according to ISCEV standard protocol recommended in 2004 or 2008<sup>40</sup> using  
18 LS-C (Mayo Co, Nagoya, Japan) and Neuropack MEB-2204 (Nihon Kohden, Tokyo,  
19 Japan). We retrospectively reviewed 529 eyes of 275 patients with RP (120 men and 155  
20 women) who underwent spectral domain (SD)-OCT scan with Spectralis (Spectralis  
21 HRA+OCT®; Heidelberg Engineering, Heidelberg, Germany) from February 2008 to

1 September 2011. In the present study, we use the term RP as to indicate progressive  
2 rod cone dystrophy, which was classified in the previous review article.<sup>41</sup> We routinely  
3 perform SD-OCT examination for patients who visited our degenerative retinal disease  
4 service at each visit. Thus, the investigated population represents almost all RP patients  
5 who visited our institution during the period. Those who showed a subnormal or  
6 non-recordable electroretinogram were included. The thinning of outer nuclear layer and  
7 the disruption of outer retinal structures including inner segment / outer segment junction  
8 depicted with SD-OCT were considered to represent retinal degeneration in the area and  
9 the findings were used to confirm the diagnosis.<sup>42</sup> We carefully excluded Leber's  
10 congenital amaurosis(LCA), cone rod dystrophy, X-linked retinoschisis, choroideremia,  
11 Stargardt disease, paraneoplastic retinopathy, or autoimmune retinopathy.

12 We further analyzed age, visual acuity, mean central foveal thickness (CFT;  $\mu\text{m}$ ),  
13 and score of mean deviation (MD) in a Humphrey field analyzer using the Mann-Whitney  
14 *U* test. Visual acuities were measured with Landolt C and were converted to the  
15 logarithm of the minimum angle of resolution (logMAR) equivalents. The Spectralis  
16 HRA+OCT has a built-in digital caliper to measure thickness or length. We measured the  
17 thickness at the center of the fovea with horizontal and vertical B-scan images, and  
18 averaged scores were used as the CFT. Humphrey field analyzer tests were performed  
19 within 6 months of OCT examination with the program of Swedish Interactive Threshold  
20 Algorithm standard 10-2.

## 21 **Measurements of Cystoid Spaces (CS)**



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1 Cross-hair scans, which consisted of horizontal and vertical 30-degree scans, centered  
2 on the fovea were obtained. Six-line over 20-degree radial scans and over 30×10-degree  
3 volume scans centered on the fovea were also obtained. Automated eye tracking and  
4 averaging was used for each measurement as follows: 100 averages for cross scans,  
5 more than 20 averages for radial scans, and more than 2 averages for volume scans.  
6 When a patient underwent serial OCT examinations, the most recent series of scans  
7 were analyzed.

8 Patients were categorized by presence or absence of CS. Patients with even a  
9 single CS were categorized as having CS. Throughout the present study, SD-OCT  
10 images were evaluated by two independent investigators (YM, AO). In cases of  
11 discrepancies, a third investigator (KO) was consulted. And we also judged the existence  
12 of epiretinal membrane (ERM) or posterior vitreous adhesion simultaneously.

13 Eyes with CS were further divided by the vertical and horizontal location of the  
14 CS. Vertically, we divided according to the layer where CS existed: ganglion cell layer  
15 (GCL), inner nuclear layer (INL) or outer nuclear layer (ONL)/OPL. When CS were found  
16 in ONL or OPL, the border between ONL and OPL became unclear, thus we categorized  
17 them together as ONL/OPL (Figure 1). Horizontally, we checked the location of CS in  
18 relation to the area with preserved outer retinal structure. The presence of ELM was  
19 considered to indicate relative preservation of outer retina. When even a single CS was  
20 noted in the area where ELM was not preserved, patients were classified as having CS  
21 outside the area of preserved outer retina (Figure 2).

## 1 **Statistical analyses of data**

2 Although we reviewed clinical records of 529 eyes of 275 patients, statistical analysis  
3 was done using one eye per one patient, because the status of right and left eyes of a  
4 patient is considerably similar.<sup>43</sup> In cases with bilateral involvement, we used the left  
5 eyes unless media opacity or poor fixation impaired the image quality. For those patients  
6 where the examination of left eye showed inadequate quality, right eyes were used for  
7 the analysis. Statistical analyses were conducted using IBM SPSS Statistics Desktop  
8 (version 19.0, IBM Japan, Tokyo, Japan). Descriptive analyses are reported as means  $\pm$   
9 standard deviation unless otherwise specified. Clinical characteristics were compared  
10 between groups using Mann-Whitney U-test or Fisher's exact test or Yates Chi-square  
11 test, as appropriate. *P* values less than 0.05 were considered statistically significant.

## 12 **RESULTS**

### 13 **Prevalence of CS**

14 CS were detected in 119 out of 529 eyes (22.5%) in 74 out of 275 patients (26.9%).  
15 Forty-five patients (60.8%) of the 74 patients had CS in both eyes. Among the studied  
16 subjects, 48 patients underwent genetic screening using microarray or direct sequencing.  
17 Mutations in EYS gene was detected in 12 patients, mutations in RHO gene were  
18 detected in 3 patients, mutations in RDS gene were detected in 2 patients, and mutation  
19 of CRX, FSCN2, ROM1, CRB1, and PDE6B were detected in one patient, respectively.  
20 Characteristics of participants are shown in Table 1. There were no significant  
21 differences between those with and without CS except for CFT ( $p < 0.001$ ). In fact, visual

1 acuity or MD measured with Humphrey perimeter in patients with or without CS showed  
2 similar distribution in scatter gram. (Figure 3) In these 74 eyes, 18 eyes were  
3 pseudophakic. Two eyes had undergone cataract surgery within one year of the  
4 examination. We excluded these two eyes from the following analysis since recent  
5 surgery might affect the development or the location of CS.<sup>44</sup> The presence of ERM or  
6 posterior vitreous adhesion was associated with the presence of CS ( $p<0.001$ ).

### 7 **Retinal location of CS**

8 We investigated the location of CS in 72 eyes of 72 patients. CS were located in  
9 GCL, INL, or ONL/OPL in all cases. Of the eyes with CS, 48 eyes (66.7%) had CS in the  
10 INL (Figure 1, A) and 18 eyes (25.0%) had CS in the INL and OPL/ONL (Figure 1, B).  
11 Five eyes had CS also in the ganglion cell layer (GCL); Three eyes (4.2%) had CS in the  
12 GCL and INL, and two eye (2.8%) had them in the GCL, INL, and OPL/ONL (Figure 1, C).  
13 Notably, CS were observed in the INL in 98.6% of investigated eyes. Only one eye  
14 (1.4%) had an isolated intra-retinal space in the ONL, however, the image in the case  
15 looked like a cleft and not a typical CS (Figure 1, D).

16 Considering the rare and atypical presentation, we excluded this case from the  
17 following analysis. We classified the rest of 71 eyes into two groups: Group 1 who had  
18 CS in the INL or in the INL and GCL (51 eyes), Group 2 who had CS in the INL and  
19 ONL/OPL or in the INL, ONL/OPL, and GCL (20 eyes). When we compared these two  
20 groups, there was no significant difference in age, foveal thickness, and MD. CFT was  
21 marginally thicker in Group 2. (Table 2)

1           We then evaluated the retinal area where CS existed. In 56 eyes of 71 eyes with  
2 CS (78.9%), CS were only found in the area where ELM was preserved, namely the area  
3 with relatively retained outer retinal structure (Figure 2, A and B). In fact, several cases  
4 showed asymmetric appearance in temporal and nasal retina, and only ipsilateral sides  
5 with preserved ELM had CS (Figure 2, B). In the remainder, CS could be seen adjacent  
6 to the remaining ELM (4 eyes, 5.6%; Figure 2, C), or in severely damaged retina with a  
7 thin RPE (6 eyes, 8.5%; Figure 2, D). Evident vitreal traction was noted in 5 of 71 eyes,  
8 in which ELM was not retained. (7.0%; Figure 2, E).

9           The presence of ERM or posterior vitreous adhesion showed no relationship with  
10 the spatial location of CS ( $p=1.000$ ).

## 11 **DISCUSSION**

12 In the present study, we showed that more than 20% of eyes with RP have retinal cysts  
13 (termed cystoids spaces (CS) in the current study). CS are predominantly distributed in  
14 the INL and in the area where the ELM is retained. The results suggest that the major  
15 source of fluid collection in CS associated with RP occurs in the inner retina. In addition,  
16 we confirm that CS associated with RP generally develop in areas of the retina that are  
17 relatively well preserved.

18           CS were detected in 22.5% of patients and 60.8% of whom had CS in both eyes.  
19 We found no difference in the prevalence of CS among each inheritance pattern and that  
20 was consistent with a previous report.<sup>45</sup> Previously reported prevalence of CME or CS in  
21 RP patients ranges from 7.4–47%.<sup>27, 31, 35, 45-49</sup> These differences in prevalence may

1 partly stem from the method used to detect CS which include fluorescein angiography  
2 (FA) or OCT. Previous reports showed the use of OCT rather than FA increases the  
3 detection rate of CS.<sup>27-29</sup> Furthermore, image resolution is better with the current model  
4 of SD-OCT,<sup>50</sup> which should further enhance detection sensitivity. The degree of CS  
5 included in prior studies may also account for these discrepancies. Some authors report  
6 the prevalence of CME based on macular involvement, and might have excluded minor  
7 parafoveal CS. Consistently, our previous work using time-domain OCT reports that the  
8 prevalence of CME was 7.5%, which would increase to 14.9% if minor CS were  
9 included.<sup>31</sup> The result strongly suggests that OCT image resolution and the inclusion  
10 criteria influences the reported prevalence of CME and highlights the need to carefully  
11 consider inclusion criteria.

12 In the present study, almost all patients (98.6%) had CS in INL. When CS were  
13 located in the GCL or ONL/OPL, they were almost always accompanied by CS in the INL.  
14 Although statistically non-significant, those with CS in the INL tended to have better  
15 visual acuity, suggesting the progression from CS in INL to INL+OPL/ONL. The frequent  
16 distribution of CS in the inner retina was in conflict with a previous report. Catier *et al.*  
17 reported that 88% of RP eyes with CME had CS in outer retinal layers.<sup>37</sup> The  
18 discrepancy may also stem from resolution of the images. In the report, the authors used  
19 OCT 2000, which was a time-domain OCT model and resolution of the image was limited  
20 in comparison to more recent models. In addition, the study only examined 8 patients,  
21 therefore, the small sample size of the study might be biased toward evident CME, which

1 would not necessarily reflect the overall characteristics of CS associated with RP.

2           The preferential inner retinal distribution of CS may shed some light on the  
3 pathology of CS in RP. Among some proposed mechanisms, the present result supports  
4 the hypothesis of Müller cell dysfunction and swelling in the primary pathogenesis of  
5 CME development.<sup>51</sup> The INL, where CS were predominantly distributed, is where Müller  
6 cell bodies exist. In addition, as discussed below, around 80% of cases only had CS  
7 located above the remaining ELM, which comprised zonula adherens of Müller cells and  
8 photoreceptors. Although the evidence is indirect, the localization of CS in the INL and in  
9 the area with preserved ELM supports the hypothesis that Müller cell dysfunction may  
10 contribute to CME development in retinal degeneration.<sup>21, 51, 52</sup>

11           The present result supports the prevailing notion that CME seems less likely to  
12 appear in the late stages of the degenerative pathology.<sup>1</sup> For example, Lupo et al.  
13 reported that RP patients with CME are younger than those with macular thinning and  
14 vitreomacular traction.<sup>34</sup> Most CS in the present study were found in areas with  
15 preserved ELM. In addition, asymmetric distribution even within an eye as shown in  
16 figure 2 suggests that CS preferentially develop in preserved areas of the retina. The  
17 pathologic process including inflammation in degenerating retina might induce fluid  
18 accumulation or the fibrotic changes in degenerated retina might prevent the formation of  
19 CS.

20           The presence of ERM or posterior vitreous adhesion was associated with the  
21 presence of CS (Table1,  $p<0.001$ ) but showed no relationship with the location of CS

1 (Table 2,  $p=1.000$ ). In instances where CS were observed in damaged areas of the retina,  
2 OCT images often showed evident vitreal traction or the CS were found to be very small.  
3 We also suggest that vitreous traction and retinal tissue loss are the major contributing  
4 factors in cases of CS in advanced RP.

5         There are several limitations to the present study. Firstly, we could not perform  
6 FA in most patients because the examination is invasive and previous reports showed  
7 that OCT is superior to FA in detecting CME.<sup>27-29</sup> The findings from FA, if available, could  
8 provide information about the involvement of inflammation or blood-retinal barrier  
9 breakdown in CS development. Secondly, morphologic observation does not provide  
10 direct evidence and other conclusions can be drawn from the observation. For example,  
11 CS in the INL may be a result of vascular leakage. Although vascular leakage does not  
12 appear to be a major contributor,<sup>53</sup> the present results do not exclude other possible  
13 mechanisms. Thirdly, genetic screening was performed in part of the subjects, which  
14 identified few causative mutations. Lastly, we could not examine the circulating  
15 anti-retinal antibodies, which were suggested to be a major cause of CS in previous  
16 report of Heckenlively and associates.<sup>16</sup>

17         In conclusion, the prevalence of CS in RP was 22.5% when using SD-OCT. They  
18 were usually observed in the INL and in areas where ELM are preserved. ERM or  
19 posterior vitreous adhesion was also associated with the presence of CS. The  
20 distribution of CS indirectly supported the involvement of Müller cells in the pathogenesis.  
21 Further studies are needed to reveal the mechanism of CS in RP.

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1 **ACKNOWLEDGEMENTS**

2 None



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Distribution of cystoid spaces in RP

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12

1 **FIGURE LEGENDS**

2

3 *Figure 1: Spectral-domain optical coherence tomography (SD-OCT) images of patients*  
4 *with cystoid spaces associated with retinitis pigmentosa.*

5 We classified the eyes into two groups according to localization of cystoid spaces (CS).  
6 (A) An image of the left eye of a 35-year-old female. CS are located only in the inner  
7 nuclear layer (INL). These cases were classified as INL group. (B) An image of the left  
8 eye of a 47-year-old male. CS are located in the INL and outer plexiform layer /outer  
9 nuclear layer (OPL/ONL). These cases were classified as INL+OPL/ONL group. (C) An  
10 image of the left eye of a 58-year-old male. CS are located in the ganglion cell layer  
11 (GCL) and INL. The patient had CS also in OPL/ONL in another scan. These cases were  
12 also classified as INL+OPL/ONL group regardless of the presence of CS in GCL. (D) An  
13 image of the left eye of a 43-year-old female. This was an exceptional case, which  
14 showed CS or cleft-like space in OPL/ONL. The case was excluded from the comparison  
15 of location. Scale bar = 200  $\mu$ m

16

17 *Figure 2: Representative spectral-domain optical coherence tomography (SD-OCT)*  
18 *images of retinitis pigmentosa (RP) patients with cystoid spaces (CS).*

19 SD-OCT revealed a correlation between the location of CS and the remaining external  
20 limiting membrane (ELM). A horizontal arrow indicates the area with remaining ELM. (A)  
21 An image of the left eye of a 35-year-old female. This is the most frequently observed  
22 pattern, which suggests that CS are predominantly located on the remaining ELM. (B) An  
23 image of the left eye of a 70-year-old female. Several cases showed similar asymmetric  
24 patterns. CS are observed only on the ipsilateral side where the ELM is preserved. (C)  
25 An image of the left eye of a 61-year-old male. Some cases (4.5%) showed CS adjacent  
26 to the remaining ELM. (D) An image of the left eye of a 18-year-old male. Some cases  
27 (9%) presented small CS where the outer retina is severely damaged. (E) An image of  
28 the left eye of a 71-year-old female. Epiretinal membrane was frequently observed in  
29 eyes with RP. Some cases were accompanied by vitreal traction as shown in the figure.  
30 Scale bar = 200  $\mu$ m

31

## Distribution of cystoid spaces in RP

1 *Figure 3: Comparison of central foveal thickness (CFT) and visual acuity (VA) or mean*  
2 *deviation (MD).*

3 The central foveal thickness was greater in the eyes with cystoid spaces (CS) but there  
4 was no significant difference in visual acuity or MD between the eyes with and without  
5 CS.  $\diamond$  represents eyes without CS and  $\blacksquare$  represents eyes with CS. Solid straight  
6 lines are the best fitting linear function for eyes without CS (logMAR VA:  $y=1.21-0.0045x$ ,  
7 MD:  $y=-35.8+0.0956x$ ) and small-dashed straight lines are the best fitting linear function  
8 for eyes with CS (logMAR VA:  $y=0.63-0.0013x$ , MD:  $y=-24.1+0.0253x$ )

1 **TABLES**

**Table 1. Comparison of Patients with Retinitis Pigmentosa with and without Cystoid Space**

	With CS	Without CS	<i>p-value</i> <sup>*1</sup>
No	74	201	
Age(years)	49.97±16.13	50.65±16.46	0.801
logMAR VA	0.29±0.49	0.37±0.57	0.624
CFT(µm)	261.59±98.24	187.03±67.94	<0.001
MD(dB)	-17.44±8.91	-18.21±10.51	0.559
Effect of ERM or posterior vitreous adhesion			
With ERM or posterior vitreous adhesion	58	78	
Without ERM or posterior vitreous adhesion	16	123	<0.001 <sup>*2</sup>
Mode of Inheritance			
AD	20	41	
AR	13	59	
X-linked	0	5	0.102 <sup>*3</sup>
Sporadic	40	89	
Unknown	1	7	

CFT: central foveal thickness; CS: cystoid spaces; MD: mean deviation; AD: autosomal dominant; AR: autosomal ressesive

\*1 Mann-whitney U test; \*2 Fisher's exact test; \*3 Chi square test

2

3



Distribution of cystoid spaces in RP

**TABLE 2. Comparison of patients with Retinitis Pigmentosa with Inner Retinal Cysts and with Inner/Outer Retinal Cysts**

	Group 1	Group 2	
	INL	INL+ONL/OPL	<i>p-value</i> <sup>*1</sup>
No	51	20	
Age(years)	48.63±16.43	52.05±15.68	0.406
logMAR VA	0.28±0.55	0.27±0.29	0.248
CFT(µm)	244.40±81.17	307.23±124.73	0.068
MD(dB)	-17.44±8.51	-17.36±9.94	0.939
Effect of ERM or posterior vitreous adhesion			
With ERM or posterior vitreous adhesion	41	16	
Without ERM or posterior vitreous adhesion	10	4	1.000 <sup>*2</sup>
mode of inheritance			
AD	13	7	
AR	10	2	
X-linked	0	0	0.648 <sup>*3</sup>
Sporadic	27	11	
Unknown	1	0	

INL: inner nuclear layer; ONL: outer nuclear layer; OPL: outer plexiform layer;  
 CFT: central foveal thickness; MD: mean deviation; AD: autosomal dominant;  
 AR: autosomal ressesive

\*1Mann-whitney U test; \*2 Fisher's exact test;\*3 Chi square test

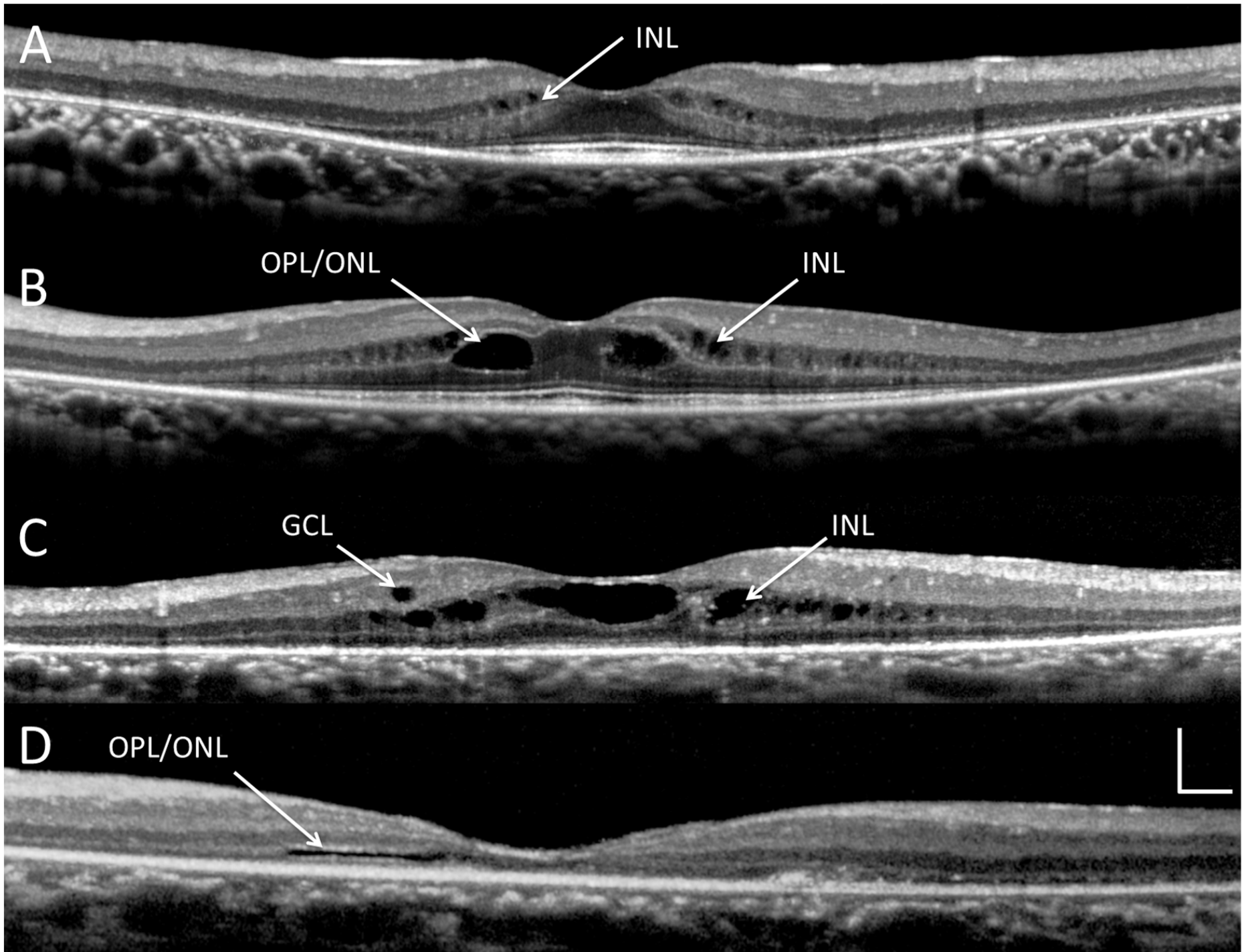


Figure 1

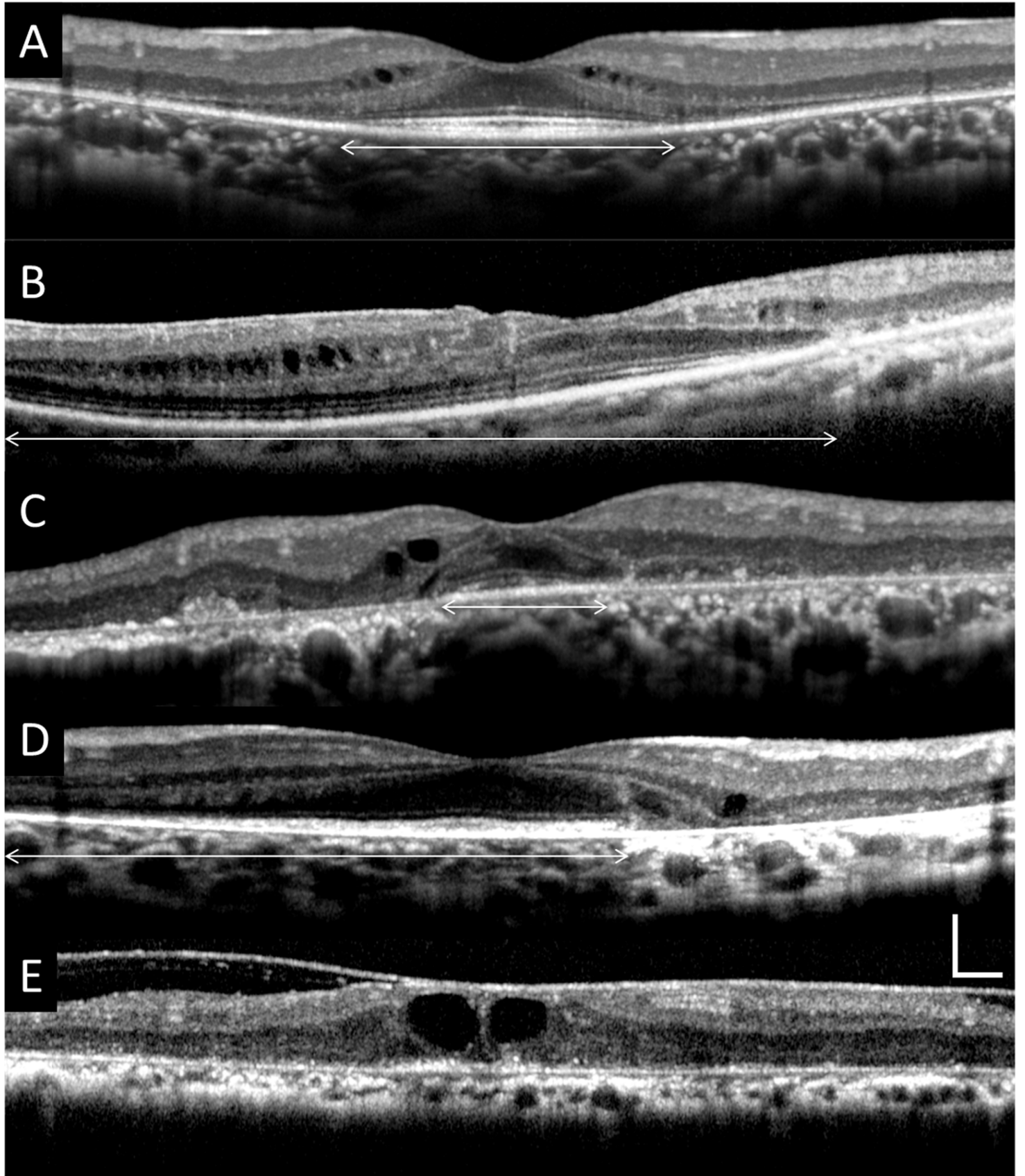


Figure 2

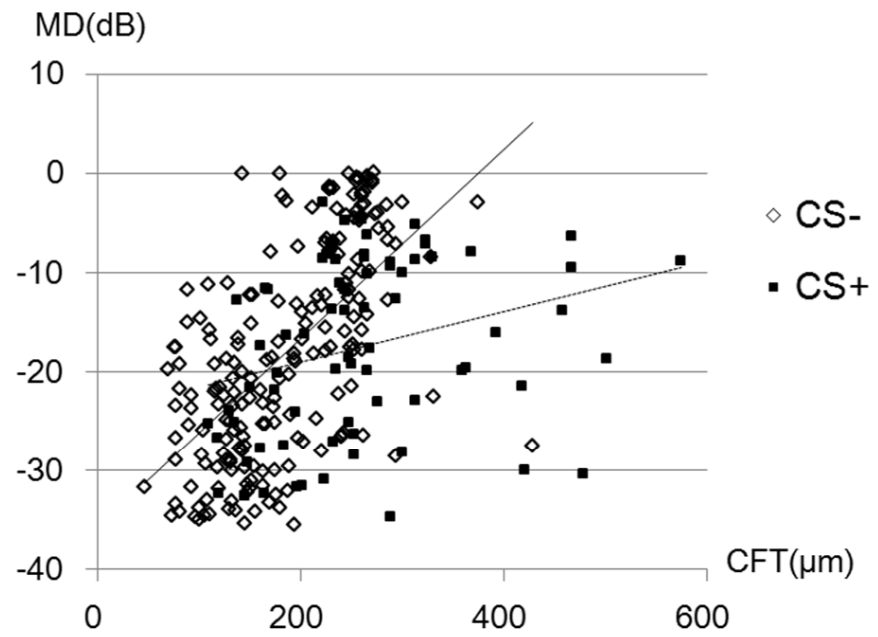
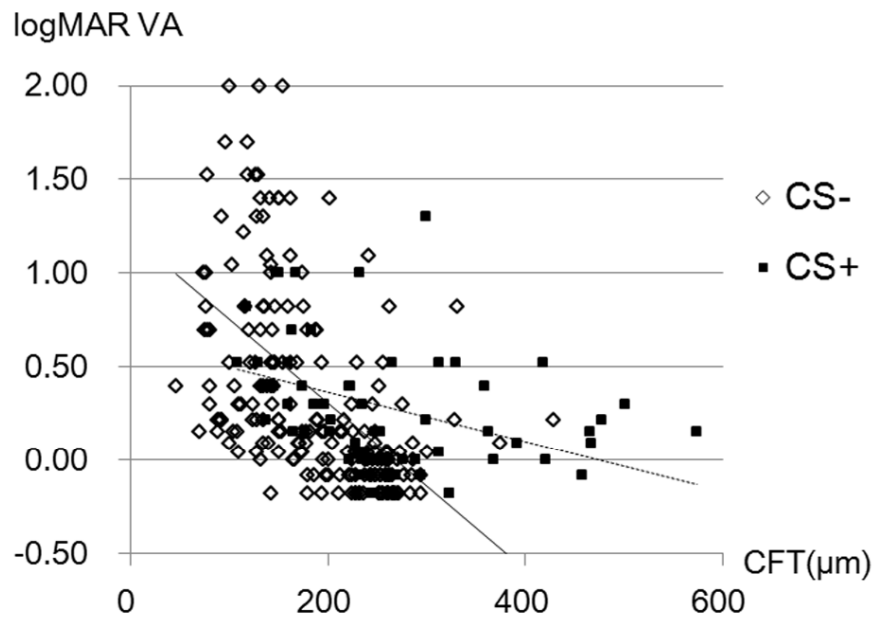


Figure 3