

Table 1. Clinical Characteristics of the Family Members With RP1L1 Mutation (p.Arg45Trp)

| Case | Age and Gender | Chief Complaint | Affected Eye | Age at Onset (Years) | Duration of Continuous Decrease in BCVA (Years) | Duration After the Onset (Years) | Systemic Disorders |
|------|----------------|---|--------------|----------------------|---|----------------------------------|--|
| 1 | 81, F | Decreased visual acuity | Bilateral* | 50 | 20 | 31 | Hypertension |
| 2 | 71, F | Decreased visual acuity and photophobia | Bilateral | 25 | 25 | 46 | Diabetes mellitus since 64 years of age |
| 3 | 74, M | Decreased visual acuity and photophobia | Bilateral | 30 | 10 | 44 | Hyperlipidemia, angina pectoris |
| 4 | 83, M | Decreased visual acuity | Bilateral | 20 | 10 | 63 | Hypertension, Multiple cerebral infarction at 73 years of age |
| 5 | 60, F | None | —† | — | — | — | — |
| 6 | 50, F | None | Bilateral* | Unknown | Unknown | Unknown | — |
| 7 | 69, F | Decreased visual acuity | Bilateral | 50 | 10 | 19 | — |
| 8 | 69, M | Decreased visual acuity and photophobia | Bilateral | 28 | 10 | 41 | Hypertension since 67 years of age, Surgery for ossification of the posterior longitudinal ligament at 45 years of age |
| 9 | 66, M | Decreased visual acuity | Bilateral | 30 | 15 | 36 | Diabetes mellitus since 63 years of age |
| 10 | 58, F | Decreased visual acuity | Bilateral | 10 | 30 | 48 | Rheumatoid arthritis since 46 years of age, Bronchiectasis since 43 years of age |
| 11 | 57, F | Decreased visual acuity | Bilateral ‡ | 47 | OD, 10, OS, still progressing | 10 | — |
| 12 | 20, M | Decreased visual acuity | Bilateral§ | 14 | Still progressing | 6 | Atopic dermatitis |
| 13 | 18, F | Decreased visual acuity | Bilateral | 6 | Still progressing | 12 | — |
| 14 | 28, M | Decreased visual acuity and photophobia | Bilateral¶ | 18 | Still progressing | 10 | — |

*Patient 1 has subjective visual disturbance only in the left eye, and Patient 6 does not have any subjective visual disturbances in both eyes. The visual dysfunction was confirmed by mfERG.

†This woman has a mutation in RP1L1, but her visual function was confirmed normal after routine examinations including mfERG.

‡This patient noticed visual disturbance only in the right eye at 47 years of age. The visual disturbance in the left eye was first noticed at 54 years of age.

§This patient noticed visual disturbance only in the left eye at 14 years of age. The visual disturbance in the right eye was first noticed at 16 years of age.

¶This patient noticed visual disturbance only in the left eye at 18 years of age. The visual disturbance in OD was first noticed at 26 years of age.

Table 2. Results of Ocular Examinations of the Family Members With RP1L1 Mutation

| Case | Age and Gender | BCVA at Final Visit | | Refraction (D)* | | Visual Field | Fundus Appearance | FA | Full-Field ERG | Relative Amplitude in mfERG at Fovea (Ring 1/Ring 5 or Ring 6)† | Other Ocular Disorders |
|------|----------------|---------------------|-------|-----------------|----------|------------------------------|-------------------|------------|--|---|--|
| | | OD | OS | OD | OS | | | | | | |
| 1 | 81, F | 1.2 | 0.1 | +4.25 | +4.625 | Relative central scotoma, OS | Normal, OU | Normal, OU | NE | 2.34, OD, 0.60, OS | Senile cataract, OU |
| 2 | 71, F | 0.4 | 0.5 | Unknown‡ | Unknown‡ | Relative central scotoma, OU | Normal, OU | NE | NE | Not measurable, OU | Cataract surgery, OS at 58 years of age, OD at 69 years of age, Ptosis, OU |
| 3 | 74, M | 0.2 | 0.3 | +2.875 | +3.375 | Relative central scotoma, OU | Normal, OU | NE | NE | Not measurable, OU | Laser peripheral iridotomy, OU at 73 years of age |
| 4 | 83, M | 0.2 | 0.2 | +1.0 | +1.625 | Relative central scotoma, OU | Normal, OU | Normal, OU | Normal ISCEV standard protocol ERG, OU | Not measurable, OU | Cataract surgery, OU at 80 years of age |
| 5 | 60, F | 1.2 | 1.2 | -0.25 | +0.875 | Normal, OU | Normal, OU | NE | NE | 4.24, OD, NE, OS | — |
| 6 | 50, F | 1.2 | 1.2 | +1.0 | +1.0 | Relative central scotoma, OU | Normal, OU | NE | NE | 2.74, OD, 2.23, OS | — |
| 7 | 69, F | 0.1§ | 0.07§ | -0.625 | +0.25 | Relative central scotoma, OU | Normal, OU | NE | Normal ISCEV standard protocol ERG, OU | Not measurable, OU | Senile cataract, OU |
| 8 | 69, M | 0.1 | 0.1 | +1.125 | +0.675 | Relative central scotoma, OU | Normal, OU | NE | Normal ISCEV standard protocol ERG, OU | 1.01, OD, 1.30, OS | — |

Table 2. (Continued)

| Case | Age and Gender | BCVA at Final Visit | | Refraction (D)* | | Visual Field | Fundus Appearance | FA | Full-Field ERG | Relative Amplitude in mfERG at Fovea (Ring 1/Ring 5 or Ring 6)† | Other Ocular Disorders |
|------|----------------|---------------------|------|-----------------|--------|------------------------------|--|------------|--|---|------------------------|
| | | OD | OS | OD | OS | | | | | | |
| 9 | 66, M | 0.2 | 0.3 | +0.125 | +0.125 | Relative central scotoma, OU | Normal, OD Background diabetic retinopathy with microaneurysm, OS | Normal, OU | Normal mixed rod-cone responses, OU | 1.21, OD1.59, OS | Senile cataract, OU |
| 10 | 58, F | 0.1 | 0.1 | +0.5 | +0.375 | Relative central scotoma, OU | Normal, OU | NE | Normal cone responses, OU | Not measurable, OU | — |
| 11 | 57, F | 0.1 | 0.4 | +0.5 | 0.0 | Relative central scotoma, OU | Normal, OU | Normal, OU | Normal ISCEV standard protocol ERG, OU | Not measurable, OU | — |
| 12 | 20, M | 0.3 | 0.3 | -0.375 | -0.75 | Relative central scotoma, OU | Normal, OU | Normal, OU | Normal ISCEV standard protocol ERG, OU | 0.98, OD1.03, OS | — |
| 13 | 18, F | 0.2 | 0.15 | -1.625‡ | -2.75‡ | Relative central scotoma, OU | Normal, OU | Normal, OU | Normal ISCEV standard protocol ERG, OU | Not measurable, OU | — |
| 14 | 28, M | 1.0 | 0.6 | -0.25 | -0.25 | Relative central scotoma, OU | Normal, OU | NE | Normal ISCEV standard protocol ERG, OU | 1.63, OD, 0.66, OS | — |

D, diopter; ISCEV, International Society of Clinical Electrophysiology and Vision; NE, not examined.

*Spherical equivalents at the initial visit.

†The responses of Ring 1 were extinguished and the N1-P1 amplitudes were not measurable in Cases 2, 3, 4, 7, 10, 11, and 13.

‡This patient had already undergone cataract surgeries for both eyes at the initial visit, and no data could be obtained about the original refraction.

§This patient's visual acuity was reduced also by senile cataract.

¶The refraction of this patient was measured after instillation of cycloplegics.

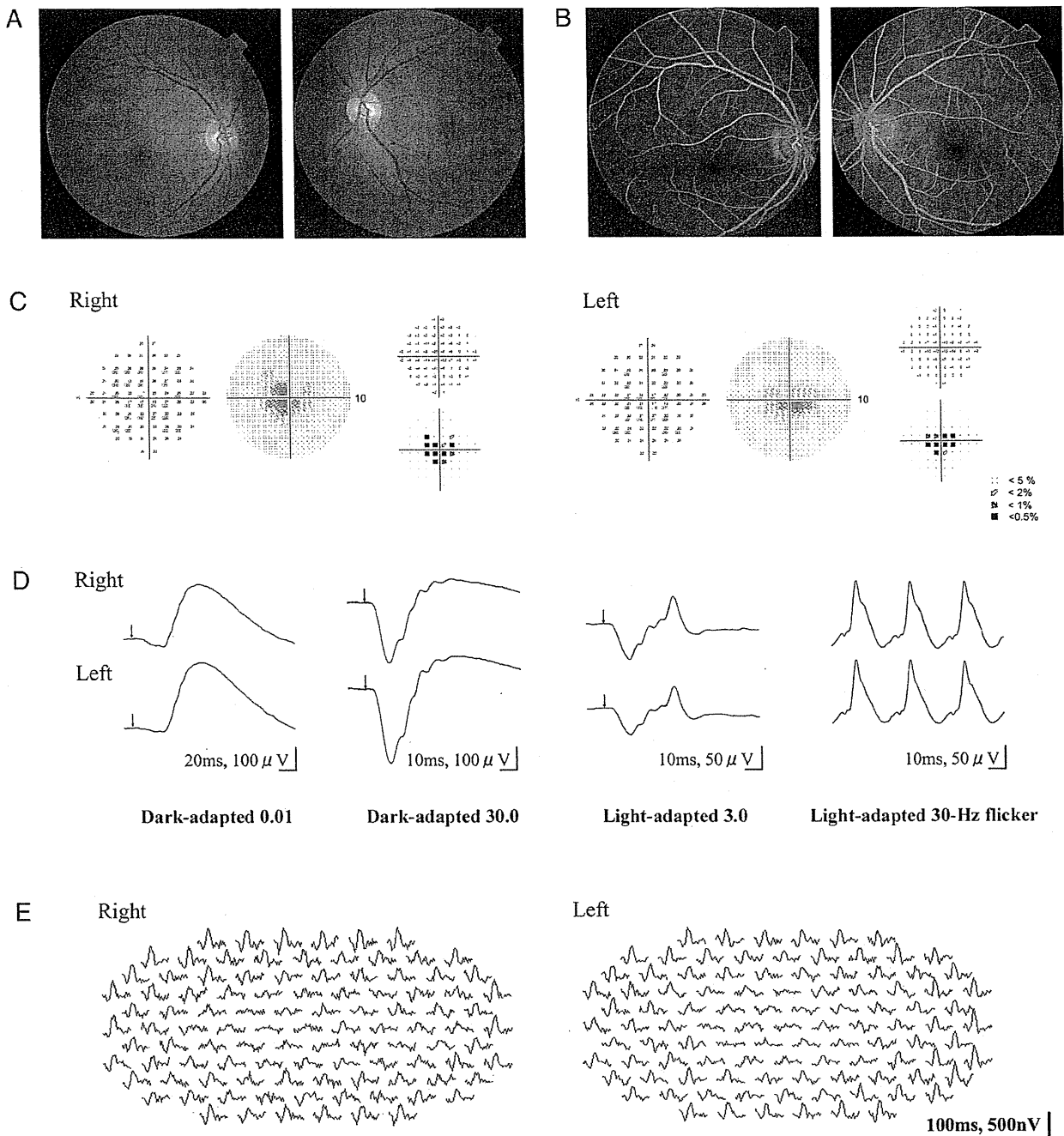


Fig. 2. Results of ocular examination of Patient 11. The data in (A) to (E) were collected 3 years after the onset of the visual disturbance at age 50 years. At this time, the patient had not noticed a decrease in the visual acuity in her left eye. The BCVA was 0.1 in the right eye and 1.2 in the right eye. **A**, and **B**. Fundus photographs and FAs showing no abnormal findings. **C**. Static visual field test (Humphrey Visual Field Analyzer, 10-2) showing relative central scotoma in both eyes. **D**. Full-field rod, mixed rod-cone, cone ERGs, and 30-Hz flicker responses. All the responses are normal in both eyes. **E**. Trace arrays of mfERGs tested with 103 hexagonal stimuli shown without spatial averaging. The responses of the central locus are extinguished in both eyes.

after the onset. This patient first noticed visual disturbances at age 20 years and was diagnosed with OMD at age 73 years. The appearance of the macula and optic disk at age 83 years was still normal >60 years after the onset of the symptoms.

Rod, mixed rod-cone, and cone full-field ERGs were recorded from 7 patients using the International Society of Clinical Electrophysiology and Vision standard protocol, and all of them showed normal rod and cone responses as in the representative case shown in

Figure 2. Only the mixed rod–cone responses were recorded from Patient 9, and only the cone responses were recorded from Patient 10, and these responses were also normal.

The amplitudes of the mfERGs were reduced in the central region of both eyes in all the 13 patients. We quantified the relative mfERG responses at the fovea by dividing the N1–P1 amplitudes of the central ring (Ring 1) by those in the outermost eccentric ring (Ring 5 in cases of 61 stimuli and Ring 6 in cases of 103 stimuli) in 13 OMD patients and 1 normal family member (Case 5) with the *RP1LI* mutation (Table 2).⁴ Among the 26 eyes of the 13 OMD patients, the N1–P1 amplitudes of the central locus were measurable in 12 eyes in 6 cases tested with the 61 stimuli. The ratio of the amplitudes of Ring 1/Ring 5 in these OMD patients ranged from 0.60 to 2.74 (average of normals: 4.34 ± 0.67 , $n = 20$). In 6 eyes tested with 61 stimuli and all the 8 eyes tested with 103 stimuli, the responses in the central locus were extinguished and the amplitudes were not measurable (see examples in Figure 2E). The ratio of the amplitudes of Ring 1/Ring 5 in a normal family member (Case 5, right eye) was 4.24, which was within the normal range.

The results of routine ocular examinations in Patient 11 at the age 50 years, when she did not have any visual disturbances in her left eye, are shown in Figure 2. The BCVA was 0.1 in the right eye and 1.2 in the left eye. The fundus and FA were normal in both eyes. Humphrey visual field tests (SITA Standard and pattern deviation 10-2) showed a relative central scotoma in both eyes. The full-field rod, mixed rod–cone, cone, and 30-Hz flicker ERGs were normal in both eyes. The mfERGs were reduced in and around the region of the central scotoma in both eyes. The Humphrey visual field test (30-2) did not detect a central scotoma in either eye (data not shown). The findings in the left eye of this patient are typical of the early stage of the OMD, where the dysfunction of the foveal region could be clearly detected in the mfERGs even though the subjective visual disturbance was almost undetectable.

Spectral-domain OCT images were recorded from 11 family members with the *RP1LI* mutation. The outer retinal structure was considered to be normal when the external limiting membrane, photoreceptor inner/outer segment (IS/OS) line, cone outer segment tip (COST) line, and retinal pigment epithelium (RPE) were clearly detected in the OCT images (Figure 3A).^{11,23}

The OCT images of 5 representative OMD patients are aligned in the order of years after the onset in Figure 3B. The right eye of Case 1, which had electrophysiologically confirmed macular dysfunction but did not have subjective visual disturbances, showed a normal IS/OS line and COST line but only at the

foveal center (asterisk in Figure 3B, ①). However, in the parafoveal region, the IS/OS line was blurred and the COST line could not be observed (arrowheads in Figure 3B, ①).

In the right eye of Case 11, the OCT images which were taken 10 years after the onset showed that the IS/OS line at the fovea was very blurred and thick but not disrupted. The COST line could not be observed in the macular area. In the perimacular region that had normal visual function, all the outer retinal structures were seen to be normal (Figure 3B, ②). Similar findings were observed in the left eye of Case 1 and the right eye of Case 8 (Figure 3B, ③ and ④).

In the right eye of Case 4, which was examined 63 years after the onset, the IS/OS line was disrupted at the fovea. The COST line could not be observed in the macula but was still visible in the perimacular region. The external limiting membrane and RPE could be observed to be normal over the entire region (Figure 3B, ⑤).

The OCT images of 2 sporadic cases of OMD without the *RP1LI* mutation are shown in Figure 3C. Both patients had a progressive central scotoma with normal-appearing fundus and normal FA. The full-field ERGs were normal but the focal macular ERGs elicited with a 10° spot were not recordable. Their OCT images, however, were not similar to those in patients with *RP1LI* mutation; the IS/OS line could be clearly observed at the fovea (Figure 3C, ① and ②), and the COST line could also be observed at the fovea, although it was slightly more blurred than in the normal cases. There was a minute disruption of the IS/OS line at the foveola in 1 case (asterisk in Figure 3C, ①).

The OCT findings in 21 eyes of 11 cases with the *RP1LI* mutation are summarized in Table 3. The examined eyes are listed in the order of years after the onset. Case 5, who was diagnosed as not having the typical characteristics of OMD, had completely normal retinal structures. In the case of OMD without subjective visual disturbances, the COST line and IS/OS line were normally observed only at the very center of the fovea (Case 1, right eye, Figure 3B, ①). In other affected cases, the COST line was not present and the IS/OS line appeared blurred in the entire fovea (Cases 14, right eye to 8). In patients with longer duration OMD, the IS/OS line was disrupted or not present as in Cases 2 and 4.

The retinal thickness at the foveola was measured as the distance from the internal limiting membrane to the inner border of the RPE. Considering the variation in the thickness in normals, we classified that the retina at the foveola was abnormally thin when the thickness was $<160 \mu\text{m}$. All the affected eyes with disease duration ≤ 12 years had normal foveal thickness (right

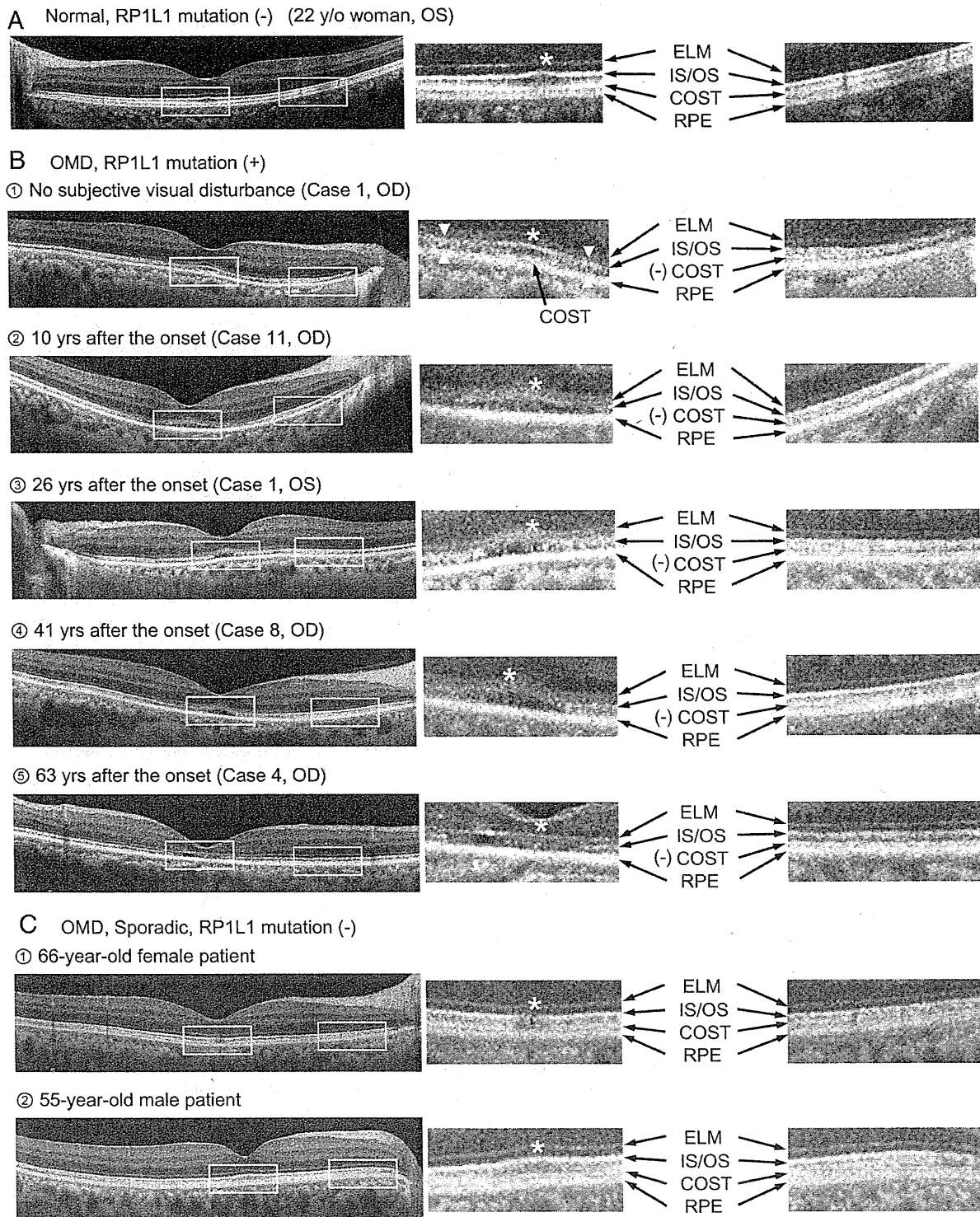


Fig. 3. Optical coherence tomography images horizontally profiled along the foveola (left) and magnified images in the fovea and the perimacular region (right). Outer retinal structures, such as external limiting membrane (ELM), photoreceptor IS/OS line, COST line, and RPE, are indicated by arrows. The foveal center is indicated by an asterisk. All the OCT images were taken with the HD-OCT (Carl Zeiss). **A.** Optical coherence tomography image of a normal control without the *RP1L1* mutation (22-year-old woman). All the outer retinal structures, for example, external limiting membrane, IS/OS line, COST line, and RPE, are clearly observed both in the fovea and the perimacular region. **B.** Optical coherence tomography images of patients affected by OMD with the *RP1L1* mutation. ①. Optical coherence tomography image of the right eye of Case 1, which did not have subjective visual disturbances. The COST line is present in the foveal center (black arrow), but not in the parafoveal region (arrowheads). The IS/OS line is clearly

eye of Cases 1 to Case 13), whereas the fovea of all the affected eyes with durations ≥ 20 years were classified as thin (Case 7 to Case 4).

To determine whether a significant correlation existed between the results of mfERGs and OCT, the relative amplitudes of the mfERGs at the fovea (Ring 1/Ring 5 or 6) are listed in Table 3. In cases where the disease durations was ≥ 3 years, the relative amplitude at the fovea was approximately 1.0 or nonrecordable because the responses of the central locus were extinguished. Only cases with very short durations had mildly reduced mfERGs in the fovea (2.34 in the right eye of Case 1 and 1.63 in the right eye of Case 14).

Discussion

Course of OMD Patients with RPILI Mutation

Our results confirmed that all the patients with the *RPILI* mutation had similar phenotypes; slowly progressive visual disturbances of both eyes, normal-appearing fundus, normal FA and full-field ERGs during the entire course of the disease, selective dysfunction at the macula detected by focal macular ERGs and mfERGs, selective abnormality of the photoreceptor layer in the macula revealed by OCT, and a final BCVA not poorer than 0.1. The age at the onset of OMD was, however, very variable among the family members and varied from 6 years to 50 years.

Our study also confirmed that there are patients with OMD who have normal visual acuity and no subjective visual disturbances until the disease progressed to a more advanced stage. Similar findings have been reported for other patients with OMD,^{1,2,24} although the etiology of these patients was not confirmed by genetic analyses. For such patients, the function of the small region in the foveola of these eyes has probably been spared so that the BCVA was normal. This was morphologically confirmed by the OCT; in the right eye of Case 1, the BCVA of which was 1.2, the OCT image showed that photoreceptor structures were spared only at the foveal center.

Among the 14 family members with the *RPILI* mutation, only Case 5 (60-year-old woman) did not

show any signs of macular dysfunction in both subjective and objective tests. Thus, this woman may be a carrier of a mutated gene, but we cannot exclude the possibility that macular dysfunction may appear later. In our genetic study of 4 other OMD families, 2 brothers (58 and 55 years old) were not diagnosed with OMD, although both had the *RPILI* mutation (p.Arg45Trp).¹² In all the OMD patients with the *RPILI* mutation, the visual dysfunction was detected no later than 50 years of age.¹²

Occult macular dystrophy has been reported to be a slowly progressive disease; however, there were no patients whose BCVA became worse than 0.1 except for Patient 7 who had an untreated senile cataract. Our results confirmed that once the BCVA is reduced to 0.1 to 0.2, the disease becomes stationary and both the subjective and objective visual functions do not deteriorate thereafter. Similarly, in 3 other families with the *RPILI* mutation, the final BCVA was not worse than 0.15 in any member.¹²

There was 1 family member (asterisk, Figure 1) who had a sudden decrease of vision in the left eye at age 49 years, but she was diagnosed with retrobulbar neuritis at the Niigata University. Her vision did not recover after steroid pulse therapy, and the optic disk gradually became atrophic. The BCVA 1 year later was 1.2 in the right eye and 0.07 in the left eye. We concluded that the vision reduction was not related to the OMD. Nakamura et al²⁵ reported a case of OMD that had normal-tension glaucoma with abnormal cupping of the optic disk. To date, the relationship between OMD and optic disk diseases has not been determined. In our family, the optic disks of all the OMD patients appeared normal, and OCT did not show any thinning of the nerve fiber layer or ganglion cell layer in any of the patients.

Diagnostic Reliabilities of mfERGs and OCT

There were patients, such as Case 6 (both eyes), Case 1 (right eye), and Case 11 (left eye), with OMD from an *RPILI* mutation who did not have any subjective visual disturbances and whose diagnosis were only confirmed by the electrophysiologic tests. These

Figure 3. (continued) observed at the foveal center (asterisk) but appears blurred in the parafoveal region (arrowheads). ②, ③, and ④. Optical coherence tomography image of the right eye of Case 11, the left eye of Case 1, and the right eye of Case 8, which show typical signs of OMD. The COST line is not present over the entire macula but is present in the perimacular regions. The IS/OS line is blurred and thick in the fovea. ⑤. Optical coherence tomography image (vertical section) of the right eye of Case 4. This image was obtained 63 years after the onset of visual symptoms. The IS/OS line is disrupted at the fovea. The COST line cannot be seen in the macula but is still visible in the perimacular region. There is an apparent thinning of the photoreceptor layer at the fovea. C. Optical coherence tomography images of sporadic cases of OMD without the *RPILI* mutation. ① and ②. Both patients had progressive central scotoma with normal-appearing fundus and normal FA. The full-field ERGs were normal but focal macular ERGs elicited by a 10° spot were not recordable. The IS/OS line could be clearly observed at the fovea in both cases, except in minute disruption at the foveola in ① (asterisk). The COST line could be observed at the fovea in both cases, although slightly more blurred than in the normal case.

Table 3. Optical Coherence Tomography Findings in 21 Eyes of 11 Family Members with RP1L1 Mutation in the Order of Years After the Onset

| Years After the Onset (Years) | Case | OD/OS | BCVA | Relative Amplitude in mfERG at fovea (Ring 1/Ring 5 or 6) | OCT Findings at Fovea | | | | Other Findings |
|-------------------------------|------|-------|------|---|--------------------------------|-------------------------------------|--------------------|---------------------------------------|--|
| | | | | | Disappearance of COST at fovea | Blurring of IS/OS Junction at Fovea | Abnormality of RPE | Thinning of Fovea (Thickness <160 μm) | |
| None | 5 | OD | 1.2 | 4.24 | - | - | - | -(217) | Not diagnosed as OMD No subjective visual disturbance |
| Unknown | 1 | OD | 1.2 | 2.34 | ±* | ±* | - | -(200) | |
| 2 | 14 | OD | 1.0 | 1.63 | + | + | - | -(160) | |
| 3 | 11 | OS | 0.4 | Not measurable | + | + | - | -(168) | |
| 6 | 12 | OD | 0.3 | 0.98 | + | + | - | -(174) | |
| | | OS | 0.3 | 1.03 | + | + | - | -(168) | |
| 10 | 14 | OS | 0.6 | 0.66 | + | + | - | -(160) | |
| 10 | 11 | OD | 0.1 | Not measurable | + | + | - | -(164) | |
| 12 | 13 | OD | 0.2 | Not measurable | + | + | - | -(181) | |
| | | OS | 0.15 | Not measurable | + | + | - | -(177) | |
| 20 | 7 | OD | 0.1 | Not measurable | + | + | - | +(134) | |
| | | OS | 0.07 | Not measurable | + | + | - | +(142) | |
| 31 | 1 | OS | 0.1 | 0.60 | + | + | - | +(150) | |
| 38 | 10 | OD | 0.1 | Not measurable | + | + | - | +(150) | |
| | | OS | 0.1 | Not measurable | + | + | - | +(153) | |
| 41 | 8 | OD | 0.1 | 1.01 | + | + | - | +(148) | |
| | | OS | 0.1 | 1.30 | + | + | - | +(148) | |
| 46 | 2 | OD | 0.4 | Not measurable | + | +† | - | +(156) | |
| | | OS | 0.5 | Not measurable | + | +† | - | +(154) | |
| 63 | 4 | OD | 0.2 | Not measurable | + | +† | - | +(77) | |
| | | OS | 0.2 | Not measurable | + | +† | - | +(76) | |

*The COST and IS/OS junction were normal only at the foveal center. In the parafovea, the COST could not be observed and the IS/OS junction was blurred.

†The IS/OS junction was disrupted at the fovea.

findings indicate that mfERGs or focal macular ERGs are sensitive enough to detect very early macular dysfunction in OMD.

Similarly, OCT could be another sensitive tool for the detection of early OMD because an abnormality of the COST line and the IO/OS line in the macula was observed in all the affected cases. However, we believe that the mfERG is more sensitive than OCT in detecting early dysfunctions of the macula in eyes with OMD. For example, Case 14 was a 28-year-old man whose BCVA was 1.0 (right eye) and 0.6 (left eye), but his fundus and visual field tests did not show any differences between the 2 eyes. He did notice a visual disturbance in his left eye 8 years before the onset in his right eye. In the OCT images, both the COST line and the IS/OS line were similarly affected for both eyes at the fovea, and the retinal thickness at the fovea was 160 μm in both eyes (Table 3). The mfERGs, on the other hand, were different in the 2 eyes; the relative amplitude of mfERG at the fovea (Ring 1/Ring 5) was 1.63 (38.2/23.5) in his right eye and 0.66 (15.8/23.8) in his left eye (Table 3). Thus, we believe that both the mfERGs and OCT can be useful in the diagnosis of OMD, but mfERGs are more reliable in detecting and evaluating minimal macular dysfunction at the early stage of the disease. The abnormalities in the OCT, however, progress slowly and continuously until the late stage, and thus they may be more useful for following the long-term progression of OMD.

Roles of *RP1L1* Gene and Occurrence of OMD

Our study confirmed that all the affected patients with *RP1L1* mutation had abnormalities of the photoreceptor structures; the IS/OS line was very blurred and thick and the COST line could not be observed in the macula (Figure 2). But in the perimacular region, which had normal visual function, all the outer retinal structures were seen to be normal. During the whole disease process, neither the external limiting membrane nor the RPE had any significant changes and remained normal. In some of sporadic cases of the OMD, similar abnormalities in the OCT could not be observed, although localized macular dysfunction was confirmed electrophysiologically (Figure 3C).

The location of COST line coincided with the location where the outer segment disks are renewed in the cones.^{23,26} The disappearance of the COST line indicates an early stage of dysfunction of the cone photoreceptors as has been found in acute zonal occult outer retinopathy.¹¹ Recently, ultrahigh-resolution OCT with adaptive optics has revealed that the IS/OS line corresponds to the ellipsoids of the photoreceptor inner segments, which are rich in mitochondria and play important roles in cellular metabolism.²⁷

Immunohistochemistry for the *RP1L1* gene in retinal section of cynomolgus monkeys showed that it was expressed in both the inner and outer segments of the rod and cone photoreceptors, although the exact site within the photoreceptor has not been confirmed.¹² *RP1L1* is believed to play important roles in the morphogenesis of photoreceptors, and once the function of *RP1L1* is disrupted by a mutation, both the electrophysiologic responses and structures of the photoreceptor can be altered. Cellular dysfunction because of an *RP1L1* mutation affects either the inner or outer segment, or both, of the photoreceptors, which first becomes apparent as an abnormality of both the COST line and IS/OS line in the OCT images.

Considering that the OCT abnormalities in sporadic cases did not show similar pattern as patients with the *RP1L1* mutation, the phenotypically confirmed OMD surely consists of diseases caused by several independent etiologies. In any case, the abnormalities in the mfERGs and OCT observed in OMD in this family strongly support the contribution of *RP1L1* mutation to the presence of this disease.

There are still some important questions of the disease process in OMD that are unsolved. First, why is only the macular region affected while the perimacular region remains intact both functionally and morphologically even at a very advanced stage? Second, why do OMD patients have normal fundus appearance until the end stage, and why does the RPE remain intact until the end stage when the photoreceptor structures are markedly damaged (Figure 3B, ⑤)? Fujinami et al²⁸ demonstrated that the fundus autofluorescence images in the macula of OMD patients are normal, indicating that the RPE is normal. Third, why does the disease progression stop when the BCVA decreases to 0.1 to 0.2?

These characteristics in the disease process are peculiar to the OMD and not observed in other macular dystrophies. More detailed investigations on the function of *RP1L1* should provide information to answer these questions.

We suggest that OMD is not a single disease caused by a specific gene mutation, *RP1L1*, but may represent different disease entities with similar retinal dysfunctions. Considering all our findings on OMD, we can phenotypically define the OMD as a slowly progressing bilateral dysfunction of the photoreceptors located in the macula, not accompanied by either vascular or RPE damage. The etiology of OMD cases without the *RP1L1* mutation is now under investigation with large number of cases and some of them might be found to be because of other autosomal recessive mutations.

Key words: electroretinography, focal macular ERG, multifocal ERG, occult macular dystrophy, optical coherence tomography, *RP1L1*.

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Analysis of *LOXLI* gene variants in Japanese patients with branch retinal vein occlusion

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Purpose: Previous studies have described a possible association between exfoliation syndrome (EX) and various ocular and systemic vascular disorders; however, the association between EX and branch retinal vein occlusion (BRVO) remains unclear. Because slit-lamp examination may overlook latent deposits of exfoliation materials, an ocular biopsy is usually needed for a precise diagnosis. We evaluated a possible association between EX and BRVO using lysyl oxidase-like 1 (*LOXLI*) gene variants as alternative markers for EX.

Methods: Allelic and genotypic frequencies of three *LOXLI* variants (rs1048661, rs3825942, and rs2165241) were determined for 78 consecutive Japanese patients with BRVO (11 patients with exfoliation syndrome [EX+], 67 patients without exfoliation syndrome [EX-]), and 158 patients with cataract without EX (CT) as controls.

Results: The rs1048661 variant differed between the BRVO and CT groups in allelic and genotypic frequencies ($p=0.0137$ and $p=0.0203$, respectively). Subgroup analysis, compared to the CT group, showed that BRVO EX+ had significantly different allelic and genotypic frequencies of rs1048661 ($p=0.00011$ and $p=0.000189$, respectively), while BRVO EX- did not ($p=0.175$ and $p=0.288$, respectively). The frequencies of rs3825942 and rs2165241 did not differ between the BRVO and CT groups.

Conclusions: No association was found between BRVO and EX if *LOXLI* variants were used as disease markers for clinically undetectable EX. The results suggested that *LOXLI* variants, well established markers for EX, are not likely genetic markers for BRVO in Japanese subjects.

Retinal vein occlusions (RVOs), including central retinal vein occlusion (CRVO), an occlusion at the central trunk of the retinal vein, and branch retinal vein occlusion (BRVO), an occlusion at an arteriovenous crossing where the retinal artery and vein are bound by a common adventitial sheath, are important causes of ocular morbidity [1,2]. Although CRVO and BRVO have several risk factors in common, including systemic hypertension, smoking, hyperlipidemia, and elevated plasma homocysteine [1,2], they do not fully explain the involvement of the central trunk or branch of the retinal vein circulation.

Exfoliation syndrome (EX), the most common identifiable cause of open-angle glaucoma worldwide, is an age-related, generalized disorder of the extracellular matrix characterized by the production and progressive accumulation of fibrillar extracellular material in many ocular tissues [3]. A recent genome-wide association study reported that one intronic single nucleotide polymorphism (SNP; rs2165241) and two exonic SNPs (rs1048661 [R141L], rs3825942 [G153D]) in the first exon of the lysyl oxidase-like 1

(*LOXLI*) gene on chromosome 15q24.1 are highly associated with EX in Icelandic and Swedish populations, and that none of these SNPs was associated with primary open-angle glaucoma in the two populations [4]. Several studies have confirmed the association of these SNPs with EX in other populations [5], including a Japanese population [6-11].

In addition to ocular tissues, production and progressive accumulation of exfoliation materials occur in skin and various visceral organs [3,12]. The association of EX with various systemic vascular and neurodegenerative disorders has been described in ischemic heart disease [13,14], carotid stiffness [15], cerebrovascular disease [16], Alzheimer disease [17], and hearing loss [18]. Regarding RVO, several studies have described a possible association between CRVO and EX diagnosed based on chart review [19], slit-lamp examination [20], histopathologic studies in enucleated eyes [21,22], and a combination of slit-lamp examination and conjunctival biopsy [23], while only a few studies have evaluated the association between BRVO and EX [19,20]. Recently, the role of the *LOXLI* polymorphism has been tested in several ocular [24] and systemic [25,26] pathologies to explore the association between EX and these pathologies, suggesting the usefulness of analyzing *LOXLI* variants as a disease marker for EX.

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TABLE 1. SUMMARY OF STUDY POPULATIONS.

| | BRVO | | | CT | p-value |
|-----------------|----------|--------|----------|----------|-------------------------|
| | Total | EX- | EX+ | | |
| No. of subjects | 78 | 67 | 11 | 158 | |
| Men/Women | | | | | |
| No. | 32/46 | 29/38 | 3/8 | 45/113 | 0.0568* |
| % | 41/59 | 33/67 | 27/73 | 28/72 | |
| Age (years) | | | | | |
| Mean±SD | 73.2±9.6 | 72±9.4 | 80.5±6.8 | 76.9±4.9 | 5.81×10 ⁻⁵ † |
| Range | 47–88 | 47–87 | 69–88 | 70–90 | |

*Fisher's exact probability test between BRVO (total) and CT groups. †Unpaired *t*-test between BRVO (total) and CT groups.

In the current study, we tested the association between *LOXLI* variants and BRVO in a Japanese population to explore a possible association between EX and BRVO.

METHODS

Subjects: Unrelated Japanese subjects with BRVO (n=78) were consecutively recruited at the Shimane University Hospital and Iinan Hospital in Shimane, Japan. The BRVO group was divided into two subgroups based on the presence (EX+, n=11) or absence (EX-, n=67) of clinically detectable ocular deposits of exfoliation material. The data set from patients with cataract without deposits of exfoliation material (CT, n=158) reported in our previous study [11] served as a control. The demographic data including age and gender for each group are summarized in Table 1.

Methods: The current study adhered to the tenets of the Declaration of Helsinki. The institutional review boards of both hospitals reviewed and approved the research. All subjects provided written informed consent. All subjects underwent a dilated pupil examination of the anterior segments, ocular media, and fundus using a slit-lamp (RO5000, Buchmann Deutschland, Düsseldorf, Germany) and a funduscope (BS-III, Neitz Instruments, Tokyo, Japan). BRVO was diagnosed if the fundus examination revealed venous dilation and tortuosity with flame-shaped and dot-blot hemorrhages in a wedge-shaped region. Patients with CRVO and hemi-CRVO were excluded. Deposits of exfoliation material were identified if the slit-lamp examination revealed a typical pattern of exfoliation material on the anterior lens surface and/or pupillary margin.

DNA genotyping: Genomic DNA was extracted from the peripheral white blood cells of each subject. A polymerase chain reaction was performed using primers designed to amplify the genomic region containing both rs1048661 and rs3825942 (forward primer: 5'-AGG TGT ACA GCT TGC TCA ACT C-3' and reverse primer: 5'-TAG TAC ACG AAA CCC TGG TCG T-3') or only rs2165241 (forward primer: 5'-AGA ATG CAA GAC CTC AGC ATG AG-3' and reverse primer: 5'-TAG TGG CCA GAG GTC TGC TAA G-3'). The sequence was determined based on the dideoxy terminator

method using an ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA) according to the manufacturer's protocol. We used SeqScape Software version 2.5 (Applied Biosystems) to analyze the sequence alignment. **Statistical analysis:** Statistical analysis was performed using R version 2.6.2. Fisher's exact test was used to compare the allele or genotype frequencies of each group with the controls.

RESULTS

The allelic and genotypic counts and frequencies of SNPs rs1048661, rs3825942, and rs2165241 within *LOXLI* are shown in Table 2. Compared to the CT group, the T allele and TT genotype frequencies of rs1048661 were higher in patients with BRVO (p=0.0137 and p=0.0203, respectively). In subgroup analysis, compared to the CT group, the group with BRVO with exfoliation material deposits (EX+) had significantly different allelic and genotypic frequencies (p=0.00011 and p=0.000189, respectively), while the group with BRVO without exfoliation material deposits (EX-) had no difference in allelic and genotypic frequencies (p=0.175 and p=0.288, respectively). Compared to the CT group, the frequencies of the G allele of rs3825942 and the C allele of rs2165241 were higher in the BRVO EX+ groups with borderline significance (p=0.0933 and p=0.0908, respectively), but the allelic and genotypic frequencies did not differ between any pairs of BRVO total or BRVO EX- and the CT group.

DISCUSSION

To the best of our knowledge, this is the first study to identify a possible association between *LOXLI* variants and BRVO. The prevalence of clinical EX increases with age, especially after age 60 [3]. Accordingly, detection of exfoliation material deposits by slit-lamp examination may overlook latent EX. Indeed, previous studies have suggested that the prevalence of exfoliation material deposits found on histopathologic assessment of ocular specimens was roughly double compared with the slit-lamp examination [27,28]. A conjunctival biopsy can detect preclinical EX that is not evident on slit-lamp examination [23]; however, because the

TABLE 2. ALLELIC AND GENOTYPIC COUNTS AND FREQUENCIES OF SNPs rs1048661, rs3825942, AND rs2165241.

| | BRVO | | | | | | | | p-value* | | |
|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-----------------|-------------------|-----------------------|
| | Total | | EX- | | EX+ | | CT | | Total versus CT | BRVO EX-versus CT | EX+ versus CT |
| | Count | Frequency | Count | Frequency | Count | Frequency | Count | Frequency | | | |
| rs1048661 | | | | | | | | | | | |
| Allele | | | | | | | | | | | |
| T | 86 | 0.566 | 67 | 0.515 | 19 | 0.864 | 140 | 0.443 | 0.0137 | 0.175 | 1.10×10 ⁻⁴ |
| G | 66 | 0.434 | 63 | 0.485 | 3 | 0.136 | 176 | 0.557 | | | |
| Genotype | | | | | | | | | | | |
| TT | 24 | 0.316 | 16 | 0.246 | 8 | 0.727 | 25 | 0.158 | 0.0203 | 0.288 | 1.89×10 ⁻⁴ |
| TG | 38 | 0.500 | 35 | 0.538 | 3 | 0.273 | 90 | 0.570 | | | |
| GG | 14 | 0.184 | 14 | 0.215 | 0 | 0 | 43 | 0.272 | | | |
| rs3825942 | | | | | | | | | | | |
| Allele | | | | | | | | | | | |
| G | 131 | 0.862 | 110 | 0.846 | 21 | 0.955 | 255 | 0.807 | 0.155 | 0.348 | 0.0933 |
| A | 21 | 0.138 | 20 | 0.154 | 1 | 0.045 | 61 | 0.193 | | | |
| Genotype | | | | | | | | | | | |
| GG | 57 | 0.750 | 47 | 0.723 | 10 | 0.909 | 101 | 0.639 | 0.212 | 0.424 | 0.209 |
| AG | 17 | 0.224 | 16 | 0.246 | 1 | 0.091 | 53 | 0.335 | | | |
| AA | 2 | 0.026 | 2 | 0.031 | 0 | 0 | 4 | 0.025 | | | |
| rs2165241 | | | | | | | | | | | |
| Allele | | | | | | | | | | | |
| C | 135 | 0.877 | 113 | 0.856 | 22 | 1.000 | 277 | 0.877 | 1 | 0.541 | 0.0908 |
| T | 19 | 0.123 | 19 | 0.144 | 0 | 0 | 39 | 0.123 | | | |
| Genotype | | | | | | | | | | | |
| CC | 61 | 0.792 | 50 | 0.758 | 11 | 1.000 | 123 | 0.778 | 0.765 | 0.685 | 0.335 |
| CT | 13 | 0.169 | 13 | 0.197 | 0 | 0 | 31 | 0.196 | | | |
| TT | 3 | 0.039 | 3 | 0.045 | 0 | 0 | 4 | 0.025 | | | |

*Fisher's exact probability test.

biopsy is invasive, it cannot be used for all patients. The role of the *LOXLI* polymorphism has been tested in several pathologies including wet and dry age-related macular degeneration and polypoidal choroidal vasculopathy in a Japanese population [24], Alzheimer disease in a Swedish population [25], and cardiovascular disease in a Hungarian population [26]. Fuse et al. found a significant association between the rs1048661 polymorphism and wet age-related macular degeneration in a Japanese population [24]. These studies encouraged us to use the *LOXLI* polymorphism as an alternative marker of clinically undetectable EX other than invasive biopsy/histopathology.

Among the three SNPs reported [4], rs1048661 has been consistently suggested as the most significant indicator of EX/glaucoma in Icelandic, Swedish, and Japanese populations [6-11]. Accordingly, our results of a significant difference in allelic and genotypic frequencies of rs1048661 between all subjects with BRVO and CT or BRVO EX+ and CT groups confirmed previous observations of the strong role of this SNP in EX. The results also suggested that using this SNP, we can detect a case-control association for EX even with such a small number of subjects (n=11) in a case group. In the same context, the other two SNPs, which showed only a borderline difference between BRVO EX+ and CT groups, may not have enough discriminatory power with this small number of subjects.

Since both the BRVO EX- and CT groups, which were classified based on slit-lamp examination as not having EX, were identical except for the presence or absence of BRVO, comparison between these two groups should provide the most reliable information about the possible role of the *LOXLI* variants in BRVO. As a result, the significant difference observed in rs1048661 between the case and control groups was canceled in the analyses between the BRVO EX- and CT groups, suggesting that the percentage of the population at risk of EX is not significantly higher in the BRVO group. A retrospective chart review reported exfoliation material deposits in 6.0% of eyes with BRVO and 6.9% of eyes with CRVO [19], suggesting a lesser extent of BRVO than CRVO in these subjects, since the BRVO/CRVO ratio was 3.2 in the general population [29]. By clinical observation of consecutive cases, the prevalence rates of EX were 8.2% in eyes with BRVO and 20.8% in eyes with CRVO compared with 5.2% in control eyes; thus the authors concluded that EX is likely a risk factor for CRVO [20]. A retrospective chart review showed that RVO occurs more frequently in eyes more affected by EX, and that the most frequent type of RVO that occurred in EX was CRVO (50%) followed by about half that prevalence of BRVO (28%) [23]. In this study, the prevalence rate of EX was 14% in eyes with BRVO from consecutive cases, which may be higher than the rate of EX in BRVO cases and normal control subjects in previous reports [19,20]. Differences in the race or age of subjects may explain the discrepancy, but this needs to be

clarified. Taken together with previous studies, our results suggest that there is no direct role of *LOXLI* variants or EX in the development of BRVO in our Japanese subjects.

In summary, we tested the possible association of *LOXLI* variants with BRVO. We did not find an association between BRVO and EX if the *LOXLI* variants were used as disease markers for clinically undetectable EX.

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