controls by excluding high myopia will improve the power for detecting a genetic association with high myopia, analysis with control 2 further decreased the significance of the association, partly because of the cohort size. Taken together with its contrasting results relative to those from the original report, we must interpret the association of SNP rs2969180 in the present study with caution.

Genetic factors influencing the risk of developing CNV in myopic eyes have been evaluated in many studies because myopic CNV is the most prominent complication leading to severe visual function loss.[35–39] Genetic variants strongly related to age-related macular degeneration (AMD), another degenerative retinal disease characterized by neovascularization in the macula, have been examined to explain the development of CNV in highly myopic eyes. However, several studies showed that susceptibility genes for AMD did not affect the occurrence of myopic CNV.[35–38] In addition, axial elongation of highly myopic eyes results in the thinning of the retina and choroid, patchy chorioretinal atrophy, and lacquer cracks, all of which are important predisposing conditions for the development of CNV.[12,40,41] Therefore, as another approach, we hypothesized that CNV could occur when the eye is affected strongly by susceptibility genes for myopia. We evaluated the genetic difference between high myopia patients with CNV and those without CNV; however, we found that genotype distribution of the SNPs evaluated did not differ significantly. Among the 5 SNPs, rs2969180 in the *SHISA6* gene showed a *P* value of 0.040, but it was not statistically significant after Bonferroni correction. Because the genetic variants contributing to high myopia and to CNV in high myopic eyes may differ, further analyses are required to assess myopic CNV independent of the susceptibility genes for myopia.

In the current study, we used genotype data in controls that were directly genotyped by arrays to eliminate a possibility of imputation error, which may affect the results. Because two SNPs, rs3138144 in *RDH5* and rs8000973 near *ZIC2*, were not genotyped directly by HumanHap610K Quad Arrays, the number of directly-genotyped control subjects in these two SNPs was smaller than that in the other 3 SNPs.

One of the possible limitations is that the current study may be that it was underpowered for detecting associations with SNPs in *RDH5* (rs3138144) and near *TOX* (rs7837791). A power calculation indicated that to obtain 80% power, we would require odds ratios of >1.22 for SNP rs3138144 and odds ratios of >1.20 for SNP rs7837791 by using the sample size used in the present study. Although we cannot estimate the odds ratios in the case-control study for high myopia, the original report showed that SNPs rs3138144 and rs7837791 had a larger effect on common myopia compared to the other 3 SNPs examined in this study,[32] thereby suggesting that these 2 SNPs required a smaller sample size for their association study. The nonsignificant associations in this study may be caused by other factors, such as heterogeneity across the populations or the discrepancy of responsible genes between common myopia and high myopia. Because the associations between these 2 SNPs and common myopia were replicated successfully in the East Asian population in the original study, these 2 SNPs may explain the difference between the mechanisms involved in the development of common myopia and high myopia. In addition, we examined only the top SNP in each susceptibility locus; therefore, our results do not necessarily negate the associations of the *RDH5* and *TOX* locus to high myopia. To investigate the contribution of these loci to myopia, more detailed, confirmatory studies with larger sample sizes are required.

In conclusion, we showed that genetic variants of SNP rs8000973 near the *ZIC2* gene and rs4778879 in the *RASGRF1* gene are associated with high myopia in Japanese subjects. This result, together with previous GWAS, implied that these SNPs may be the susceptibility loci for myopia and high myopia. However, we were not able to identify genetic factors influencing CNV risk in high myopic patients among these 5 SNPs.

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Appendix

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Reduction of Retinal Sensitivity in Eyes With Reticular Pseudodrusen

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• PURPOSE: To evaluate the effect of macular reticular pseudodrusen on retinal function using multiple imaging methods.

• DESIGN: Prospective cross-sectional study.

• METHODS: Thirteen eyes with reticular pseudodrusen, but without any other macular abnormality or glaucoma, and 20 normal eyes were evaluated. All subjects underwent color fundus photography, infrared reflectance (IR), fundus autofluorescence (FAF), and microperimetry.

• RESULTS: The similarity in the number of reticular pseudodrusen was evaluated through inter-observer intraclass correlation coefficients, which ranged from 0.852-0.944. IR could detect reticular pseudodrusen within the center circle area in 12 eyes, whereas blue-channel fundus photography and FAF could only detect these lesions in 1 and 3 eyes, respectively. The number of reticular pseudodrusen correlated among the different imaging modalities ($P < .001$ for all) for all areas of the macula, except the center. The mean retinal sensitivity in eyes with reticular pseudodrusen was lower in all areas of the macula, compared with normal eyes ($P < .001$ for all). The number of reticular pseudodrusen correlated with retinal sensitivity in all areas by IR imaging ($P = .003$, $P < .001$, $P = .003$ for center, inner ring, outer ring, respectively), in the inner and outer rings by blue-channel fundus photography ($P < .001$ for both), and in the inner and outer rings by FAF ($P < .001$ and $P = .001$, respectively).

• CONCLUSIONS: Although multiple imaging modalities are capable of quantifying reticular pseudodrusen, IR appears to have the best ability to do so as compared to blue-channel photography and FAF. The distribution and number of reticular pseudodrusen lesions are closely associated with retinal sensitivity. (Am J Ophthalmol 2013;156:1184–1191. © 2013 by Elsevier Inc. All rights reserved.)

R ETICULAR PSEUDODRUSEN WERE FIRST IDENTIFIED as distinctive yellowish patterns in the macula of patients with age-related macular degeneration (AMD) by using blue-light fundus photography.[1] Arnold and associates described a yellowish interlacing network of oval or roundish lesions, termed reticular pseudodrusen, with a diameter of 125-250 μm that were detected in red-free fundus photography.[2] Recently, reticular pseudodrusen have been recognized as an additional distinctive morphologic feature of AMD.[3] Several reports have suggested that reticular pseudodrusen are associated with a high risk of progression to late-stage AMD.[4–8]

The development of new imaging methods, such as confocal scanning-laser ophthalmoscopy (SLO) and spectral-domain optical coherence tomography (SDOCT), has led to the determination of the exact location of reticular pseudodrusen and to additional insight into its pathogenesis.[8–21] Using SDOCT, several researchers have suggested that the hyperreflective material above the retinal pigment epithelium (RPE) may alter photoreceptor structures in eyes with reticular pseudodrusen,[9,15] implying that reticular pseudodrusen may have an influence on retinal function. However, understanding of the relationship between reticular pseudodrusen and retinal function has been limited, and further investigation for comprehending such relationship is required.

The purpose of this study was to evaluate the effect of the presence of macular reticular pseudodrusen on retinal function by using multiple imaging methods, including fundus photography, infrared reflectance (IR), fundus autofluorescence (FAF), and fundus-monitoring microperimetry (MP). Although several terminologies have been used to describe this clinical feature,[2,9,14] we use the term "reticular pseudodrusen" according to the nomenclature promoted by Arnold and associates.[2]

METHODS

ALL OF THE STUDY INVESTIGATIONS ADHERED TO THE tenets of the Declaration of Helsinki, and this study was approved by the Institutional Review Board and the Ethics Committee of Kyoto University Graduate School of Medicine. The nature of the study, the implications of participating in this research study, and its possible consequences were explained to the study candidates, after

which a written informed consent was obtained from all participants.

• PARTICIPANTS: Candidates in this prospective cross-sectional study were patients with reticular pseudodrusen, but without any other macular abnormality or glaucoma, who visited the Kyoto University Hospital, Kyoto, Japan, between February 2011 and March 2013, as well as healthy volunteers.

All of the patient eyes had already been classified as having reticular pseudodrusen on the basis of the appearance of reticular patterns in at least 2 imaging modalities, including the blue-channel images obtained using color fundus photography, IR, FAF, indocyanine green angiography, and SDOCT.[8,16] Eyes with conventional drusen (hard/soft drusen), cuticular drusen, pigment epithelial detachment, serous retinal detachment, choroidal neovascularization (ie, neovasucular AMD, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation), or geographic atrophy were excluded from this study. Eyes with other macular abnormalities (ie, pathologic myopia, idiopathic choroidal neovascularization, angioid streaks, other secondary choroidal neovascularization, central serous chorioretinopathy, epiretinal membranes, or retinal arterial macroaneurysms) or any history or signs of retinal surgery, including laser treatment, were also excluded from this study.

• MULTIMODAL IMAGING METHODS: All subjects underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA), determination of intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy with a noncontact lens, color fundus photography, IR, FAF, and MP during the same visit.

Color fundus photographs (field, 40 degrees) were obtained digitally using a Topcon TRC NW6S nonmydriatic retinal camera (Topcon, Tokyo, Japan) after medical dilation of the pupil (phenylephrine, 0.5% and tropicamide, 0.5%). To examine the blue-channel images, ImageJ software (National Institutes of Health, Bethesda, Maryland, USA) was used to display the individual color channels (red, green, and blue) of the photographs. Adjustment was performed automatically by using the ImageJ software before grading. IR and FAF images were acquired using a confocal SLO (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). The IR images were obtained using a light stimulus at a wavelength of 820 nm. The FAF images were obtained using an excitation light with a wavelength of 488 nm and a barrier filter beginning at 500 nm. The field of view was set to 30 × 30 degrees, centered on the macula. Adjustment of brightness and contrast for IR and FAF images was performed automatically by using the ImageJ software before grading.

The quality of each image was evaluated by an experienced observer and only eyes with adequate image quality from each imaging modality were included.
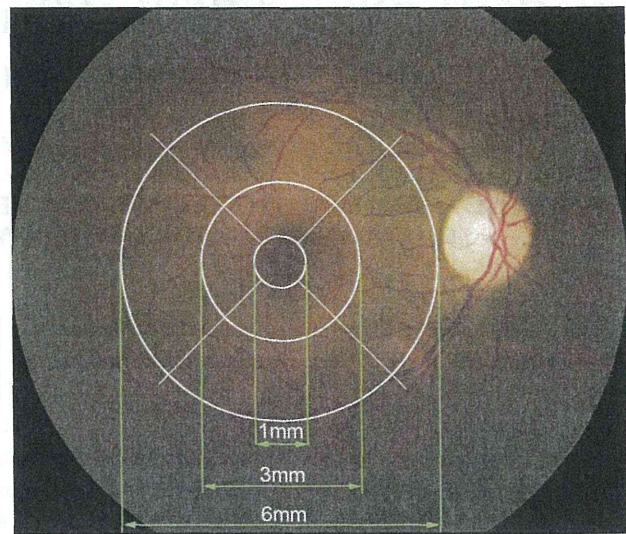

FIGURE 1. Early Treatment Diabetic Retinopathy Study sector. Delineation of the 9 macular sectors, according to the Early Treatment Diabetic Retinopathy Study (ETDRS), within which we measured the number of reticular pseudodrusen.

• QUANTIFICATION OF THE RETICULAR PSEUDODRUSEN: In the blue-channel contrast-enhanced color fundus photography, the reticular pattern was identified as light flecks.[2] Reticular IR was defined as a group of hyporeflectant or halo-like (hyperreflectant lesions surrounded by hyporeflective rings) lesions against a background of mild hyperreflectance.[14] Reticular autofluorescence was defined as a group of hypofluorescent or halo-like lesions against a background of mildly elevated AF.[11,13] The number of flecks in the blue-channel fundus photography images, hyporeflectant or halo-like lesions on IR, and hypoautofluorescent or halo-like lesions on FAF in 9 separate macular areas (based on the Early Treatment Diabetic Retinopathy Study [ETDRS] sectors [Figure 1]) were determined by 2 experienced observers using a cell-count tool built into ImageJ. The center of the fovea was determined to be the center of the foveal avascular zone on each image, before grading. The numbers of each lesion were determined as the mean of the number determined by the 2 graders; if the values reported were significantly different between the graders, a third grader was invited to determine the number of lesions and the value closest to that determined by the third grader was selected.

• MICROPERIMETRY: We used fundus-monitoring MP to measure retinal sensitivity. MP-1 software (NIDEK, Padova, Italy) was set to automatically track eye movements and to evaluate every acquired frame for shifts in the directions of the x and y axes of the fundus, with respect to a reference image obtained by an infrared camera at the beginning of the examination.

We used a 4-2-staircase strategy with Goldmann size III stimuli against a white background with an illumination of
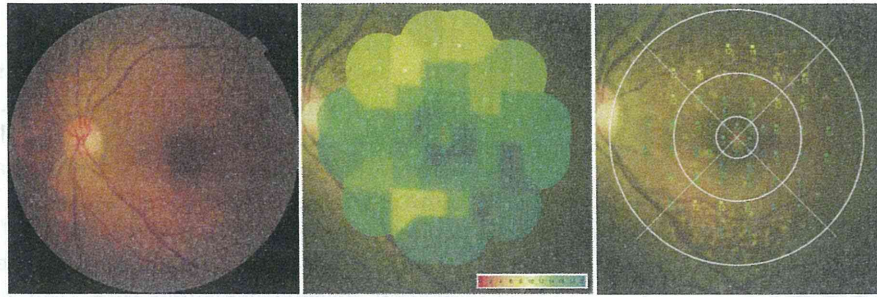
FIGURE 2. Reticular pseudodrusen and retinal sensitivity in the macula. Images of the left eye of a 55-year-old woman with reticular pseudodrusen but without any macular abnormalities. Her Snellen-equivalent best-corrected visual acuity was 20/15. (Left) Color fundus photography shows numerous reticular pseudodrusen. (Middle) Colored map image of microperimetry. Green indicates normal, and yellow indicates decreased retinal sensitivity. (Right) Retinal sensitivity map image merged with the ETDRS scale. Retinal sensitivity is decreased in the area with reticular pseudodrusen.

1.27 cd/m^2 to examine 57 stimulus locations covering the central 20 degrees (designed to probe photopic vision). Differential luminance, defined as the difference between the stimulus luminance and the background luminance, was 127 cd/m^2 at 0-dB stimulation, and the maximum stimulus attenuation was 20 dB; the stimulus duration was 200 ms. The mean retinal sensitivity was calculated in 9 separate areas, based on ETDRS sectors, within the macula (Figure 2). Retinal sensitivity on the border between sectors was included in the counterclockwise sector.

• STATISTICAL ANALYSES: BCVA, measured using the Landolt chart, was expressed as the Snellen equivalent or the logarithm of the minimal angle of resolution (logMAR). For inter-observer measurements, 2-way mixed, average measure intraclass correlation coefficients (ICC [3, K]) were obtained. For comparing the variables among areas, the Bonferroni correction was used. We calculated the Pearson product moment correlation coefficient to determine associations between mean retinal sensitivity and the number of reticular pseudodrusen in each sector. All statistical evaluations were performed in SPSS v.17 (SPSS, Chicago, Illinois, USA). Significance was defined as $P < .05$.

RESULTS

FIFTEEN CONSECUTIVE EYES WITH RETICULAR PSEUDODRU-sen but without any other macular abnormality or glaucoma were examined. Among them, 2 eyes were excluded because of the poor image quality. Thus 13 eyes from 10 patients were included in this study. Twenty normal eyes in 20 subjects were included as control. The ages of the subjects ranged from 55-86 years (mean ± SD, 71.6 ± 9.4 years) for patients with reticular pseudodrusen and from 65-79 years (mean ± SD, 70.2 ± 4.8 years) for normal volunteers ($P = .200$).

TABLE 1. Reproducibility of the Determination of the Number of Reticular Pseudodrusen in the Macula Using Different Imaging Modalities

Imaging	Inter-observer Intraclass Correlation Coefficients		
	Center	Inner Ring[b]	Outer Ring[b]
Fundus photography[a]	0.919	0.852	0.854
IR	0.930	0.939	0.944
FAF	0.906	0.923	0.920

FAF = fundus autofluorescence; IR = infrared reflectance.
[a]Blue channel of fundus photography.
[b]Center, central fovea (1 mm); Inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

The BCVA of patients with reticular pseudodrusen ranged from 20/32-20/12 (mean logMAR = −0.04 ± 0.10), and 11 eyes (85%) had BCVA ≥ 20/20. The spherical equivalent refractive error ranged from −1.25 to +1.75 diopter.

The reproducibility of the determination of the number of reticular pseudodrusen (the light flecks in blue-channel fundus photographs, the hyporeflectant or halo-like lesions in IR images, and the hypofluorescent or halo-like lesions in FAF images) was evaluated through an inter-observer ICC; the ICC ranged from 0.852-0.944. The ICCs of each region, obtained by each imaging method, are shown in Table 1 and the Supplemental Table (available at AJO. com) (using log values).

The mean numbers of reticular pseudodrusen in each macular ETDRS sector are shown in Table 2. Reticular pseudodrusen were most frequently detected in the superior area by each modality (Figure 3). In the outer ring, the reticular pseudodrusen were found in greater numbers in the superior side than in the temporal side ($P = .039$, $P = .020$, and $P < .001$ for blue-channel fundus photography, IR, and FAF, respectively, with Bonferroni correction), the inferior side ($P = .081$, $P = .044$, and $P = .001$ for blue-channel fundus photography, IR, and FAF,

TABLE 2. Mean Number of Reticular Pseudodrusen in Macular Early Treatment Diabetic Retinopathy Study Sectors Using Different Imaging Modalities

Imaging	Center[b]	Inner Ring[b]				Outer Ring[b]				Whole Macula
		Superior	Inferior	Nasal	Temporal	Superior	Inferior	Nasal	Temporal	
Fundus photography[a]	1.8 ± 5.7	30.0 ± 21.4	24.9 ± 28.6	18.0 ± 16.1	16.4 ± 20.8	103.3 ± 65.2	42.4 ± 52.2	34.3 ± 44.7	35.6 ± 45.0	306.7 ± 270.2
IR	12.9 ± 11.5	42.2 ± 17.2	27.0 ± 21.0	29.8 ± 21.9	30.0 ± 25.4	92.5 ± 41.1	47.5 ± 43.6	44.3 ± 38.3	42.9 ± 40.7	369.3 ± 219.1
FAF	0.5 ± 1.0	20.1 ± 13.4	17.3 ± 13.1	18.5 ± 15.4	16.2 ± 14.5	78.1 ± 28.3	32.7 ± 26.9	18.5 ± 15.5	30.4 ± 29.0	247.7 ± 132.6

FAF = fundus autofluorescence; IR = infrared reflectance.

Values are mean ± standard deviation.

[a]Blue channel of fundus photography.

[b]Center, central fovea (1 mm); inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

respectively, with Bonferroni correction), or the nasal side ($P = .034$, $P = .026$, and $P = .001$ for blue-channel fundus photography, IR, and FAF, respectively, with Bonferroni correction). IR could reveal reticular pseudodrusen within the center circle area (1 mm diameter) in 12 eyes (92%), whereas blue-channel fundus photography and FAF could only detect their presence in 1 (8%) or 3 eyes (23%), respectively ($P < .001$, χ^2 test; Figure 3, Table 2). The number of reticular pseudodrusen correlated among the different imaging modalities ($P < .001$ for all), except for the center area (Figure 3, Table 3).

Table 4 shows the mean retinal sensitivity in each ETDRS sector. In normal eyes, the mean retinal sensitivity was > 16.0 dB in each ETDRS sector, though it was slightly lower in the superior area of the outer ring (Table 4). The mean retinal sensitivity in eyes with reticular pseudodrusen was lower in all areas of the macula, compared with normal eyes ($P < .001$ for all). In eyes with reticular pseudodrusen, the mean retinal sensitivity of the whole macula was 12.9 ± 3.9 dB, but the mean retinal sensitivity in the superior side was significantly lower compared with the inferior side ($P = .001$, with Bonferroni correction), the temporal side ($P = .006$, with Bonferroni correction), and the nasal side ($P = .020$, with Bonferroni correction) of the outer ring (Figures 2 and 3).

The extent of the effect of decreased sensitivity was identical to reticular pseudodrusen distribution. The reduction in retinal sensitivity was most severe in the superior area of the outer ring (48.5% reduction as compared with the controls) in eyes with reticular pseudodrusen, whereas it was least in the central area (20.7% reduction as compared with the controls) (Table 4).

The number of reticular pseudodrusen correlated with the retinal sensitivity determined in each area by IR imaging ($P = .003$, $P < .001$, and $P = .003$ for center, inner ring, and outer ring, respectively), in the inner and outer rings in blue-channel fundus photographs ($P < .001$ for both), and in the inner and outer rings by FAF ($P < .001$ and $P = .001$, respectively; Figure 3, Table 5). Thus, the lesion number did not correlate significantly with sensitivity in the central sector for FAF and blue-channel fundus photographs, but did for IR images.

DISCUSSION

RETICULAR PSEUDODRUSEN HAVE TRADITIONALLY BEEN identified with blue-light fundus photography. However, recent studies have suggested that additional imaging modalities, such as IR, FAF, indocyanine green angiography imaging, and SDOCT, would facilitate the identification of these interlacing networks.[4,5,8–10,13–17] Using SDOCT, Zweifel and associates suggested the hyperreflective material could be graded by the thickness of the accumulation above the RPE and their
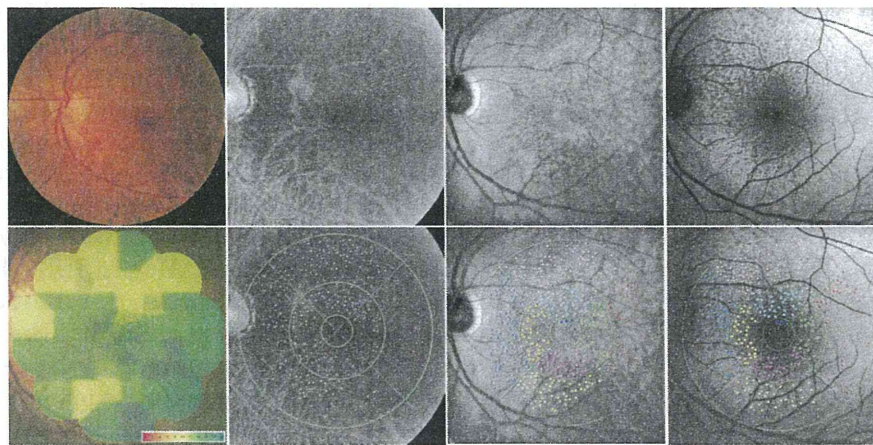
Imaging	Center	Inner ring				Outer ring				Whole Macula
		Superior	Inferior	Nasal	Temporal	Superior	Inferior	Nasal	Temporal	
Fundus photography	0	36	27	23	14	78	26	39	16	259
IR	5	46	40	35	31	91	54	67	35	404
FAF	3	38	28	34	21	102	32	62	26	346

FIGURE 3. Quantification of reticular pseudodrusen using multimodal imaging and relationship with retinal sensitivity in the macula. Images of the left eye of a 74-year-old man with reticular pseudodrusen but without any macular abnormalities. His Snellen-equivalent best-corrected visual acuity was 20/15. (Upper row, left) Color fundus photography shows numerous reticular pseudodrusen. (Upper row, middle-left) On the blue-channel of contrast-enhanced color fundus photography, the reticular pattern is identified as light flecks. (Upper row, middle-right) On infrared reflectance (IR) imaging, reticular pseudodrusen are identified as a group of hyporeflectant lesions or halo-like lesions against a background of mild hyperreflectance. (Upper row, right) In fundus autofluorescence (FAF) imaging, reticular pseudodrusen are identified as a group of hypofluorescent lesions or halo-like lesions against a background of mildly elevated FAF. (Lower row, left) Microperimetry (MP) results. Retinal sensitivity is decreased in the superior, nasal, and inferior sides of the fovea. (Lower row, middle and right) Reticular pseudodrusen labeling results of the blue-channel of fundus photography (Lower row, middle-left), IR (Lower row, middle-right), and FAF (Lower row, right). Note that reticular pseudodrusen are frequently seen in the area where retinal sensitivity is decreased in MP. The color coding for the spots was used to show each area of the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. (Bottom) Table shows the number of reticular pseudodrusen in macular ETDRS sectors using each imaging modality.

TABLE 3. Correlation of the Observed Number of Reticular Pseudodrusen in the Macula, Using the Different Imaging Modalities

Imaging	Area[b]	IR	Fundus photography[a]
Fundus photography[a]	Center	.343 (0.336)	
	Inner ring	<.001 (0.798)	
	Outer ring	<.001 (0.834)	
FAF	Center	.617 (0.153)	.007 (0.784)
	Inner ring	<.001 (0.667)	<.001 (0.544)
	Outer ring	<.001 (0.882)	<.001 (0.737)

FAF = fundus autofluorescence; IR = infrared reflectance.
Data presented as P value (correlation coefficient). Bold indicates statistical significance.
[a]Blue channel of fundus photography.
[b]Center, central fovea (1 mm); inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

breakthrough into the inner and outer segment junction (IS/OS) of the photoreceptor, in later stages.[9] Querques and associates analyzed the progression of reticular pseudodrusen using SDOCT and found that the hyperreflective material faded because of reabsorption and migration within the inner retinal layers during the last stage of the disease.[15] These reports suggest that the subretinal material above the RPE in eyes with reticular pseudodrusen may alter photoreceptor structure. In the current study, we investigated how the distribution of reticular pseudodrusen affected retinal sensitivity by using multiple imaging modalities.

Several studies have revealed that reticular pseudodrusen lesions are seen most frequently in and near the superior arcades.[14,16] Consistent with these reports, the current study showed that these lesions were most frequently detected in the superior portion of the outer macula by all of the modalities. In addition, IR could detect reticular pseudodrusen within the center circle area in most eyes,

TABLE 4. Mean Retinal Sensitivity in Normal Eyes vs Eyes With Reticular Pseudodrusen in the Macular Early Treatment Diabetic Retinopathy Study Sectors

	Center[b]	Inner Ring[b]				Outer Ring[b]				Whole Macula
		Superior	Inferior	Nasal	Temporal	Superior	Inferior	Nasal	Temporal	
Normal (n = 20)	17.9 ± 1.9	18.1 ± 1.3	19.0 ± 1.3	18.9 ± 1.3	18.7 ± 1.4	16.3 ± 1.5	18.6 ± 1.1	17.8 ± 1.5	18.1 ± 1.2	18.2 ± 1.1
RPD (n = 13)	14.2 ± 3.3	11.5 ± 4.9	14.9 ± 3.5	14.8 ± 3.4	14.1 ± 2.8	8.4 ± 3.7	13.6 ± 2.8	12.2 ± 3.4	12.7 ± 2.7	12.9 ± 3.9
RPD/normal (%)	79.3	63.5	78.4	78.3	75.4	51.5	73.1	68.5	69.3	70.9
P[a]	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

FAF = fundus autofluorescence; IR = infrared reflectance; RPD = reticular pseudodrusen.
Values are mean ± standard deviation (dB) unless otherwise indicated. Bold indicates statistical significance.
[a]t test.
[b]Center, central fovea (1 mm); inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

whereas blue-channel fundus photography and FAF could detect these lesions in the center circles of only a few eyes, similar to the results of Smith and associates.[14] These authors reported that the region associated with the lesions, as detected by IR, was the central, 1-mm-diameter zone in 52% of affected eyes; FAF and color fundus images never found lesions in the central zone.[14] In most eyes, the central macula is observed to be dark by blue-channel fundus photography and FAF, using SLO. Thus, the evaluation of reticular pseudodrusen, near the fovea, is difficult when using these imaging methods. These results suggest thatIR imaging is necessary for the visualization and quantification of reticular pseudodrusen in the central macula.

The number of reticular pseudodrusen correlated well among the different imaging modalities, except for those in the center area. However, more reticular pseudodrusen were also detected by IR even in the inner and outer ring sectors. These results suggest that the flecks observed by fundus photography and the hypofluorescent lesions observed by FAF and IR reflect identical reticular pseudodrusen lesions, although the sensitivity for detecting the lesions is different among the methods. In fact, several researchers have reported that IR imaging has superior sensitivity compared with that of blue-channel fundus photography.[9,14,16] Compared with IR, blue-channel fundus photography and FAF imaging may be hampered to a greater extent by media opacity because of the short wavelengths being used, giving these modalities a lower sensitivity of detecting the lesions than IR.

The mean retinal sensitivity in eyes with reticular pseudodrusen was lower in all areas of the macula, compared with normal eyes. The mean retinal sensitivity in the superior side, where reticular pseudodrusen lesions were most frequently seen, was significantly lower than that for any other side. In addition, the number of reticular pseudodrusen correlated with the detected retinal sensitivity in each area, by each imaging modality. All these results suggest that the distribution and number of reticular pseudodrusen lesions are closely associated with the reduction of retinal sensitivity. Recently, Curcio and associates reported on the morphology, prevalence, and topography of subretinal drusenoid deposits (SDD), a candidate histologic correlate of reticular pseudodrusen, in donor eyes with non-neovascular AMD.[22] In 1 specimen from their study, photoreceptor morphology was disrupted by SDD formations, manifest as outer segment shortening and loss of inner segment deflection.[22] Migration of subretinal material into neurosensory retina has been reported histologically.[23] These results suggest that reticular pseudodrusen may cause damage to the adjacent photoreceptors, resulting in a reduction of retinal sensitivity. Thus, ophthalmologists should be aware that reticular pseudodrusen not only are a risk factor for late AMD,[4-8] but may also cause retinal dysfunction.

To date, there have been few reports about the relationship between reticular pseudodrusen and retinal function. Recently, Alten and associates evaluated the effect of reticular pseudodrusen on retinal function by multifocal

TABLE 5. Correlation of the Number of Reticular Pseudodrusen With Macular Retinal Sensitivity, Using the Different Imaging Modalities

Imaging	Area[b]	Correlation Coefficient	P[c]
Fundus photography[a]	Center	−0.437	.206
	Inner ring	−0.632	**<.001**
	Outer ring	−0.496	**<.001**
IR	Center	−0.760	**.003**
	Inner ring	−0.619	**<.001**
	Outer ring	−0.409	**.003**
FAF	Center	−0.246	.418
	Inner ring	−0.532	**<.001**
	Outer ring	−0.465	**.001**

FAF = fundus autofluorescence; IR = infrared reflectance.
Bold indicates statistical significance.
[a]Blue channel of fundus photography.
[b]Center = central fovea (1 mm); inner ring = 1-3 mm from the central fovea; outer ring = 3-6 mm from the central fovea.
[c]P value using Pearson correlation coefficient.

electroretinography (mfERG) in 19 eyes.[24] They reported that mfERG measurements did not show a definite influence of these lesions on electrophysiological activity in the areas affected exclusively by reticular pseudodrusen,[23] inconsistent with the current study. One possible explanation for the discrepancy may be that the main mfERG signals are derived from cones, and reticular pseudodrusen are present primarily in the outer macula, where cones are sparse and rods are abundant. Curcio and associates proposed a hypothesis that rods may play an important role as a pathophysiological stimulus for the formation of SDD.[22] Thus rods, rather than cones, may have a close relationship with retinal sensitivity reduction in eyes with reticular pseudodrusen.

The effects of conventional drusen on visual function are controversial.[25,26] There was no decrease in the sensitivity of eyes with soft drusen over the drusen in one study; however, the results of another study were different. Iwama and associates[26] reported that mean retinal sensitivity was lower (61.8%-82.6%) than that of the intact retina in areas with confluent soft drusen. In the present study, we have shown that mean retinal sensitivity was lower (51.5%-79.3%) than that in normal controls in the entire macular area of eyes with reticular pseudodrusen.

Our study has several limitations. First, this study included a relatively small sample size, which also involves binocular cases accordingly, mostly because of practical limitations associated with the rarity of "pure" reticular pseudodrusen; most eyes with reticular pseudodrusen (90% of patients in our institution) also demonstrate other macular abnormalities such as soft drusen, choroidal neovascularization, or geographic atrophy.[8] Second, MP-1 can only test more central regions, and therefore cannot be used to evaluate peripheral areas. Reticular pseudodrusen was observed outside the vascular arcades and on the nasal side of the disc. Thus, further investigation of the wider areas is required. Third, reticular pseudodrusen are sometimes branching or confluent;[19] thus, the number of reticular pseudodrusen might have been underestimated, and the quantification might be rather subjective. However, reticular pseudodrusen were identified with a more punctate appearance within the macular area, compared with outside the macula. In addition, the inter-observer reproducibility was high in the current study. Fourth, because this was a cross-sectional study, we might have overlooked stage 4 reticular pseudodrusen (fading of the subretinal material because of reabsorption and migration within the inner retinal layers), reported by Querques and associates.[15] Longitudinal studies are needed to evaluate the last stage of reticular pseudodrusen development.

In conclusion, we have shown that the number of reticular pseudodrusen is related to retinal sensitivity, based on different types of imaging. In the future, longitudinal studies need to be conducted to learn more about the involvement of reticular pseudodrusen pathogenesis on retinal function. Cumulatively, such studies should facilitate improved management of this disease.

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