related macular degeneration and other causes: update. Retina 2005;25(2):119–134.
41. Yamashiro K, Tsujikawa A, Nishida A, Mandai M, Kurimoto Y. Recurrence of polypoidal choroidal vasculopathy after photodynamic therapy. Jpn J Ophthalmol 2008;52(6):457–462.
42. Schmidt-Erfurth U, Schlötzer-Schrehard U, Cursiefen C, Michels S, Beckendorf A, Naumann GO. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. Invest Ophthalmol Vis Sci 2003; 44(10):4473–4480.
43. Sakurada Y, Kubota T, Imasawa M, Mabuchi F, Tanabe N, Iijima H. Association of LOC387715 A69S genotype with visual prognosis after photodynamic therapy for polypoidal choroidal vasculopathy. Retina 2010;30(10):1616–1621.
44. Nakata I, Yamashiro K, Yamada R, et al. Genetic variants in pigment epithelium-derived factor influence response of polypoidal choroidal vasculopathy to photodynamic therapy. Ophthalmology 2011;118(7):1408–1415.
45. Hirami Y, Tsujikawa A, Otani A, et al. Hemorrhagic complications after photodynamic therapy for polypoidal choroidal vasculopathy. Retina 2007;27(3):335–341.
46. Ojima Y, Tsujikawa A, Otani A, Hirami Y, Aikawa H, Yoshimura N. Recurrent bleeding after photodynamic therapy in polypoidal choroidal vasculopathy. Am J Ophthalmol 2006;141(5):958–960.

REPORTING VISUAL ACUITIES

The AJO encourages authors to report the visual acuity in the manuscript using the same nomenclature that was used in gathering the data provided they were recorded in one of the methods listed here. This table of equivalent visual acuities is provided to the readers as an aid to interpret visual acuity findings in familiar units.

Table of Equivalent Visual Acuity Measurements

Snellen Visual Acuities				
4 Meters	6 Meters	20 Feet	Decimal Fraction	LogMAR
4/40	6/60	20/200	0.10	+1.0
4/32	6/48	20/160	0.125	+0.9
4/25	6/38	20/125	0.16	+0.8
4/20	6/30	20/100	0.20	+0.7
4/16	6/24	20/80	0.25	+0.6
4/12.6	6/20	20/63	0.32	+0.5
4/10	6/15	20/50	0.40	+0.4
4/8	6/12	20/40	0.50	+0.3
4/6.3	6/10	20/32	0.63	+0.2
4/5	6/7.5	20/25	0.80	+0.1
4/4	6/6	20/20	1.00	0.0
4/3.2	6/5	20/16	1.25	−0.1
4/2.5	6/3.75	20/12.5	1.60	−0.2
4/2	6/3	20/10	2.00	−0.3

From Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94:91–96.

Biosketch

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Prevalence and Genomic Association of Reticular Pseudodrusen in Age-Related Macular Degeneration

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• PURPOSE: To survey the prevalence of reticular pseudodrusen in late age-related macular degeneration (AMD) using multiple imaging methods, and to investigate the association between reticular pseudodrusen and polymorphisms in complement factor H (*CFH*) and age-related maculopathy susceptibility 2 (*ARMS2*) genes.

• DESIGN: Retrospective case series.

• METHODS: This study included 216 consecutive patients with late AMD (typical AMD, polypoidal choroidal vasculopathy [PCV], retinal angiomatous proliferation [RAP], or geographic atrophy). Eyes were assessed for reticular pseudodrusen using the blue channel of color fundus photography, infrared reflectance, fundus autofluorescence, and spectral-domain optical coherence tomography. The major AMD-associated single nucleotide polymorphisms (*CFH* Y402 rs1061170, *CFH* I62 V rs800292, and *ARMS2* A69S rs10490924) were genotyped.

• RESULTS: Forty-nine eyes of 30 patients had a reticular pattern in ≥2 imaging modalities and were diagnosed with reticular pseudodrusen. Of these, 16 had bilateral late AMD, whereas 32 of 186 patients without reticular pseudodrusen had bilateral late AMD ($P < .001$). The prevalence of reticular pseudodrusen was 83% in RAP, 50% in geographic atrophy, 9% in typical AMD, and 2% in PCV. The frequency of the T allele in *ARMS2* A69S in patients with and without reticular pseudodrusen was 78.6% and 59.9%, respectively ($P = .007$).

• CONCLUSIONS: The prevalence of reticular pseudodrusen was low in PCV cases. About 50% of patients with reticular pseudodrusen had bilateral late AMD. The connection of *ARMS2* risk allele and reticular pseudodrusen was confirmed in a Japanese population. (Am J Ophthalmol 2013;155:260–269. © 2013 by Elsevier Inc. All rights reserved.)

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RETICULAR DRUSEN, DESCRIBED IN THE WISCONSIN Grading System as one type of drusen that form ill-defined networks of broad interlacing ribbons, were first identified using blue-light fundus photography.[1,2] Arnold and associates described a yellowish interlacing network of oval-shaped or roundish lesions, termed reticular pseudodrusen, with a diameter of 125–250 μm that were seen in red-free fundus photography and infrared scanning-laser ophthalmoscopy (SLO).[3] Recently, reticular pseudodrusen have been recognized as an additional distinctive morphologic feature observed in age-related macular degeneration (AMD).[4] Furthermore, several reports have suggested that reticular pseudodrusen are associated with a high risk of progression to late AMD.[5–8] In the longitudinal Beaver Dam Eye Study, reticular pseudodrusen were found to confer a high risk of progression to late-stage AMD, with twice the risk compared with eyes with soft drusen.[8]

The development of new imaging methods, such as confocal SLO and spectral-domain optical coherence tomography (SD OCT), has led to improvements in diagnosing reticular pseudodrusen.[4,7–14] Previous reports showed that near-infrared reflectance (IR), fundus autofluorescence (FAF), and SD OCT were more useful than conventional fundus photography to detect reticular pseudodrusen and suggested that the assessment of reticular pseudodrusen should involve multiple imaging methods.[4,7-10,13,14]

Existing evidence suggests an association of AMD with polymorphisms in the complement factor H (*CFH*) gene and age-related maculopathy susceptibility 2 (*ARMS2*) gene.[15-24] Among the various polymorphisms, the Y402H and I62V variants in the *CFH* gene and the A69S variant in the *ARMS2* gene have been reported to show an association with AMD.[15-24] Recently an association between reticular pseudodrusen and polymorphisms in these genes has been reported.[8,25] Klein and associates showed that the prevalence of reticular pseudodrusen was higher in those homozygous (CC) or heterozygous (TC) for *CFH* Y402H than in those without this variant (TT).[8] On the other hand, Smith and associates demonstrated that *CFH* Y402H risk variant was significantly associated with the absence of reticular macular disease but enhanced risk for reticular macular disease was conferred by the *ARMS2* A69S risk allele.[25] Thus, to date, the association between reticular pseudodrusen and genomic

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background has not reached a consensus. In addition, little is known about the distribution of reticular pseudodrusen in each AMD subtype.

The purpose of this study was to survey the prevalence of reticular pseudodrusen in late AMD using multiple imaging methods and, moreover, to investigate the association of high-risk alleles in the *CFH* (Y402H, rs1061170 and I62V, rs800292) and *ARMS2* (A69S, rs10490924) genes with reticular pseudodrusen. Several terminologies have been used to describe this clinical feature.[2,3,9,14] In this report, we use the term "reticular pseudodrusen" according to the nomenclature by Arnold and associates.[3]

METHODS

WE RETROSPECTIVELY REVIEWED THE MEDICAL RECORDS OF 249 consecutive patients with newly diagnosed late AMD who first visited the Macular Service at Kyoto University Hospital between August 3, 2009 and July 21, 2011. Subjects included in this study were ≥50 years of age and had either typical AMD, polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP), or geographic atrophy. The diagnosis of PCV was based on the indocyanine green angiography (IA) showing a branching vascular network terminating in polypoidal swelling. The diagnosis of RAP was based on the criteria of Yannuzzi and associates[26] via fundus photography, fluorescein angiography (FA), IA, and SD OCT. Neovascular AMD other than PCV or RAP was defined as typical AMD. Geographic atrophy was defined using color fundus photography as a sharply delineated area (at least 175 μm in diameter) of hypopigmentation, depigmentation, or apparent absence of the retinal pigment epithelium (RPE) in which choroidal vessels were clearly visible. Eyes with other macular abnormalities (ie, pathologic myopia, idiopathic choroidal neovascularization, presumed ocular histoplasmosis, angioid streaks, other secondary choroidal neovascularization, central serous chorioretinopathy, epiretinal membrane, or retinal arterial macroaneurysm) were excluded from this study. All diagnoses were made by 3 retinal specialists (S.O., K.Y., and A.T.) who observed the images together and discussed each case; however, a fourth specialist (N.Y.) was consulted in case of a disagreement between the 3 initial reviewers. The fourth specialist made a decision in 13 of the 249 patients (5.2%). Patients were included only if at least 3 specialists agreed on the diagnosis.

All study investigations adhered to the tenets of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board and the Ethics Committee of Kyoto University Graduate School of Medicine prior to the study. Written informed consent was obtained from all patients who were genotyped. Because this was a retrospective study, written informed consent for research participation was not obtained, but the nature of this study was explained on our website.

• MULTIMODAL IMAGING METHODS: All patients underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity, determination of intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy with a noncontact lens, color fundus photography, SD OCT, IR, FAF, FA, and IA.

Color fundus photographs (field, 30-40 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 of the color photography, ImageJ software (National Institutes of Health, Bethesda, Maryland, USA) was used to display the individual color channels (red, green, and blue) of the obtained photographs. In ImageJ, the command path of Image > Color > Split Channels was used. Subsequently, the command path of Image > Adjust > Brightness/Contrast was used if needed. Adjustment was performed automatically using the ImageJ software before grading.

IR, FAF, FA, and IA images were acquired using a confocal SLO (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). The IR images were obtained using a light stimulus of 820 nm. The FAF images were obtained using an excitation light 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.

SD OCT was conducted using a Spectralis HRA+OCT (Heidelberg Engineering). First, horizontal and vertical line scans through the fovea center were obtained at a 30-degree angle, followed by serial horizontal scans with an examination field size ranging from 30 × 10 degrees to 30 × 25 degrees, depending on the case. At each location of interest on the retina, 50 SD OCT images were acquired and averaged to reduce speckle noise.

• DEFINITION OF THE RETICULAR PSEUDODRUSEN USING MULTIMODAL IMAGING: First, the quality of each image was evaluated by an experienced ophthalmologist (N.U.A.) and patients with adequate image quality in both eyes were included. Image quality was evaluated twice on all other days, and only images having an eligible quality during both evaluations were used. All these images were evaluated for the detection of reticular pseudodrusen by 2 independent experienced ophthalmologists (N.U.A. and S.O.). The evaluation of each image was performed referring to the corresponding images obtained from other imaging modalities. FA images were also referred to in order to distinguish reticular drusen from other lesions such as basal laminar drusen. In case of any discrepancy, a third experienced ophthalmologist (A.T.) was asked to arbitrate. In the current study, eyes diagnosed as having reticular pseudodrusen were those with reticular patterns in more than 2 of the following: the blue channel image

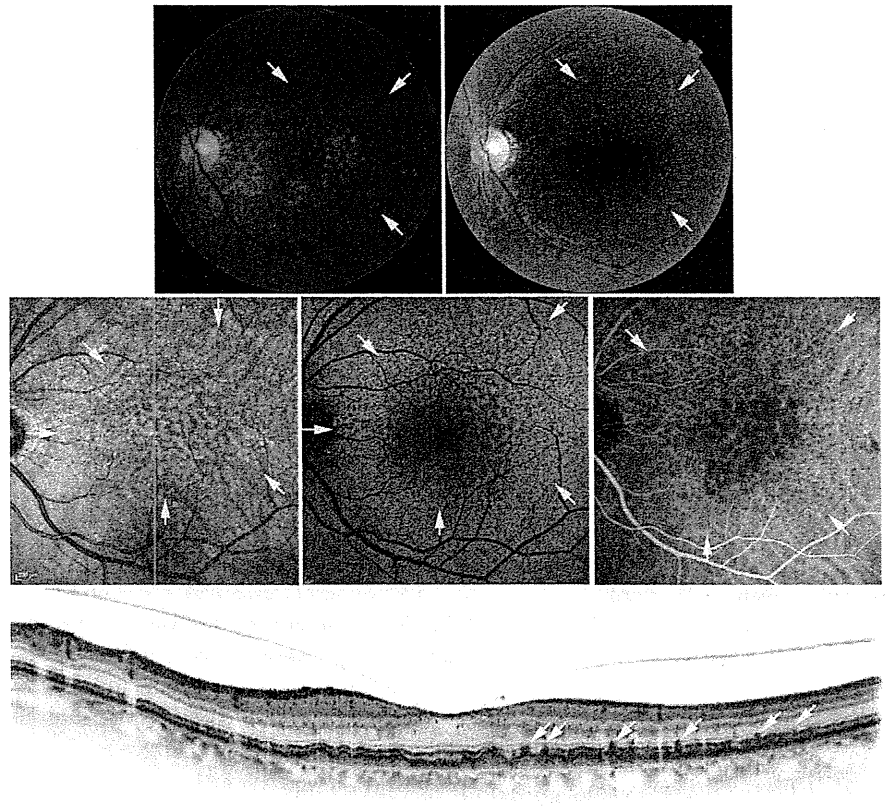

FIGURE 1. Reticular patterns in late age-related macular degeneration in multimodal imaging. (Top row, left) Color fundus photography. (Top row, right) Blue channel of contrast-enhanced color fundus photography. For color fundus or the corresponding blue channel of contrast-enhanced color fundus photography, reticular pattern is identified as light interlacing networks (arrows). (Second row, left) Infrared reflectance (IR). Reticular IR is identified as a grouping of hyporeflectant lesions against a background of mild hyperreflectance with analogous characteristics (arrows). (Second row, middle) Fundus autofluorescence (FAF). Reticular FAF is identified as a grouping of ill-defined, hypofluorescent lesions against a background of mildly elevated FAF (arrows). (Second row, right) Indocyanine green angiography (late phase). A pattern of hyporeflective dots is seen (arrows) corresponding to the reticular pattern in color fundus photography. (Bottom) Spectral-domain optical coherence tomography (SD OCT). Vertical line scan thorough the fovea in the direction of the green arrow in Second row, left shows reticular lesions identified as hyperreflective mounds or triangular lesions above the retinal pigment epithelium (arrows).

of color fundus photography, IR, FAF, or SD OCT. For the blue channel of contrast-enhanced color fundus photography, a reticular pattern was identified as light interlacing networks that were 125-250 μm wide (Figure 1).[3] Reticular autofluorescence was defined as a group of ill-defined, hypofluorescent lesions against a background of mildly elevated AF (Figure 1).[11,13] Reticular IR was defined as a group of hyporeflectant lesions against a background of mild hyperreflectance with analogous characteristics (Figure 1).[14] SD OCT reticular lesions were defined as ≥5 hyperreflective mounds or triangular lesions above the RPE in ≥1 B-scan (Figure 1).[10]

• GENOTYPING: Genomic DNA was prepared from leukocytes of peripheral blood with a DNA extraction kit (QuickGene-610L; Fujifilm, Tokyo, Japan). Of the 216 patients who met the inclusion criteria, genomic data from 11 patients were not available because of the following reasons: (1) consensus of blood extraction was not achieved; (2) genotyping was not possible because of the preservation state. Thus, analyses for genomic data were limited to 205 patients. We genotyped the major AMD-associated single nucleotide polymorphism (SNP), *CFH* Y402 rs1061170, I62 V rs800292, and *ARMS2* A69S rs10490924. The SNPs were genotyped using TaqMan SNP assays with the ABI PRISM 7700 system (Applied Biosystems Inc, Foster City, California, USA), according to the manufacturer's instructions.

• STATISTICAL ANALYSIS: Statistical analysis was performed using SPSS 17 software (SPSS Inc, Chicago, Illinois, USA). All values are presented as a mean ± standard deviation (SD). For statistical analysis, visual acuity measured using a Landolt chart was converted to the logarithm of the minimal angle of resolution (logMAR). Mann-Whitney *U* tests were used to compare data from 2 groups

TABLE 1. Characteristics of Patients With Late Age-Related Macular Degeneration in This Study

	Typical AMD	PCV	RAP	Geographic Atrophy	Combined[a]	Total
No. of patients (%)	97 (44.9)	87 (40.2)	12 (5.6)	12 (5.6)	8 (3.7)	216 (100)
Sex, n (%)						
Men	76 (78)	70 (80)	4 (33)	7 (58)	4 (50)	161 (75)
Women	21 (22)	17 (20)	8 (67)	5 (42)	4 (50)	55 (25)
No. of affected eyes (%)						
Two	17 (18)	9 (10)	5 (42)	9 (75)	8	48 (22)
One	80 (82)	78 (90)	7 (58)	3 (25)		168 (78)
Age (mean ± SD)	74.8 ± 8.3	71.5 ± 8.4	81.3 ± 8.2	72.3 ± 9.3	82.3 ± 2.9	73.9 ± 8.7

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; SD = standard deviation.

[a]Patients with typical AMD, PCV, RAP, or geographic atrophy in 1 eye and another type of AMD in the other eye (4 typical AMD and PCV, 1 typical AMD and RAP, 1 typical AMD and geographic atrophy, 1 geographic atrophy and RAP, and 1 geographic atrophy and PCV).

in which normal distributions were not verified. To compare ratios between the 2 groups, χ^2 tests were used. $P < .05$ was considered statistically significant.

RESULTS

IN THIS STUDY, DATA OF 249 CONSECUTIVE PATIENTS WITH late AMD were retrospectively reviewed; however, 5 patients with an eye with phthisis bulbi and 28 patients with poor image quality were excluded. (The intraobserver agreement for grading of image quality was 94.6%.) Thus, 216 patients were included in this study. All patients were Japanese. The patients comprised 161 men and 55 women, aged 51-92 years (mean ± SD, 73.9 ± 8.7). Among them, 97 patients (44.9%) had typical AMD, 87 (40.2%) had PCV, 12 (5.6%) had RAP, and 12 (5.6%) had geographic atrophy. Eight patients had a different type of late AMD in both eyes that was defined as "combined." (Four patients had typical AMD in 1 eye and PCV in the other eye. The other combinations were typical AMD and geographic atrophy, typical AMD and RAP, geographic atrophy and PCV, and geographic atrophy and RAP. The visual acuity of these patients ranged from 20/2000 to 20/12 (mean logMAR = 0.33 ± 0.52). Spherical equivalent refractive error ranged from -5.50 diopters (D) to +4.50 D in the eyes with late AMD, and ranged from -18.375 D to +3.875 D in the fellow eyes without late AMD (4 eyes with high myopia [<-6 D] were included in the fellow eyes). Sixty-eight eyes had pseudophakia. The characteristics of the participants are summarized in Table 1.

Using color fundus photography, IR, FAF, or SD OCT, it was determined that out of 432 eyes, 30 eyes (6.9%), 65 eyes (15.0%), 45 eyes (10.4%), and 47 eyes (10.9%), respectively, had a reticular pattern. (Inter- and intraobserver agreements for grading for the detection of reticular pseudodrusen are shown in Table 2.) Furthermore, 49 eyes (11.3%) of 30 patients had a reticular pattern according to ≥2 imaging modalities, and were defined as having reticular pseudodrusen. Reticular pseudodrusen was confirmed bilaterally in 19 of these 30 patients (63.3%) and unilaterally in 11 patients (36.7%). In all 11 patients with unilateral reticular pseudodrusen, the other eye had neovascular AMD (4 were RAP, 6 were typical AMD, and 1 was PCV). In 38 of 49 eyes (77.6%) with reticular pseudodrusen, a pattern of hyporeflective dots was detected in the middle- and late-phase IA corresponding to the reticular pattern detected in IR and FAF (Figure 1).

The characteristics of patients with reticular pseudodrusen (30 patients [13.9%]) and patients without reticular pseudodrusen (186 patients) are summarized in Tables 3 and 4, respectively. Of the 30 patients with reticular pseudodrusen, 19 (63.3%) were women, whereas only 36 of 186 patients without reticular pseudodrusen (19.4%) were women ($P < .001$, χ^2 test). The mean age of the patients with reticular pseudodrusen was 80.6 ± 6.8 years (range, 65-92 years), which was significantly higher than that of patients without reticular pseudodrusen (72.8 ± 8.5 years; range, 51-92 years; $P < .001$, Mann-Whitney test). In addition, 16 of 30 patients with reticular pseudodrusen (53.3%) had bilateral late AMD, whereas only 32 of 186 patients without reticular pseudodrusen (17.2%) had bilateral late AMD ($P < .001$, χ^2 test). In patients over 70 years old, 15 of 28 patients with reticular pseudodrusen (53.6%) had bilateral late AMD, whereas 26 of 118 patients without reticular pseudodrusen (22.0%) had bilateral late AMD ($P = .001$, χ^2 test).

The prevalence rate of reticular pseudodrusen was different according to the disease type of late AMD: 10 of 12 patients with RAP (83.3%), 6 of 12 patients with geographic atrophy (50.0%), 9 of 97 patients with typical AMD (9.2%), 2 of 87 patients with PCV (2.2%), and 3 of 8 patients with combined subtype (Table 5). In patients over 70 years old, the prevalence of reticular pseudodrusen was 10 of 11 patients with RAP (90.9%), 5 of 7 patients

TABLE 2. Intra- and Interobserver Agreements for Grading of the Detection of Reticular Pseudodrusen in Late Age-Related Macular Degeneration

	Blue Channel[a]	IR	FAF	SD OCT
Intraobserver agreements				
Accordance rate (%)	96.9	94.6	95.3	98.3
Kappa coef cient (95% con dence interval)	0.72 (0.57-0.86)	0.78 (0.69-0.86)	0.74 (0.63-0.85)	0.91 (0.85-0.98)
Interobserver agreements				
Accordance rate (%)	94.7	91.4	91.2	97.9
Kappa coef cient (95% con dence interval)	0.62 (0.47-0.76)	0.64 (0.54-0.75)	0.61 (0.50-0.72)	0.89 (0.81-0.96)

FAF = fundus auto uorescence; IR = near-infrared re ectance; SD OCT = spectral-domain optical coherence tomography.
[a]Blue channel of color fundus photography.

TABLE 3. Characteristics of Patients With Reticular Pseudodrusen in Late Age-Related Macular Degeneration

	Typical AMD	PCV	RAP	Geographic Atrophy	Combined[a]	Total
No. of patients	9	2	10	6	3	30
Sex, n (%)						
Men	5 (56)	0	3 (30)	2 (33)	1 (33)	11 (37)
Women	4 (44)	2 (100)	7 (70)	4 (67)	2 (67)	19 (63)
No. of eyes with AMD (%)						
Two	3 (33)	0 (0)	4 (40)	6 (100)	3	16 (53)
One	6 (67)	2 (100)	6 (60)	0 (0)		14 (47)
Age (mean ± SD)	79.1 ± 6.6	82.0 ± 4.2	82.4 ± 7.7	78.3 ± 8.0	83.0 ± 2.6	80.6 ± 6.8

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; SD = standard deviation.
[a]Patients with typical AMD, PCV, RAP, or geographic atrophy in 1 eye and another type of AMD in the other eye (1 RAP and GA, 1 AMD and RAP, and 1 AMD and PCV).

with geographic atrophy (71.4%), 8 of 67 patients with typical AMD (11.9%), and 2 of 53 patients with PCV (3.8%) (Supplemental Table, available at AJO.com).

In 28 patients with reticular pseudodrusen and 177 patients without reticular pseudodrusen, the frequency of the minor allele in *CFH* I62 V polymorphism was 21.4% and 23.0%, respectively (Table 6). Upon analyzing the genotype, we determined the G allele did not contribute to reticular pseudodrusen ($P = .865$). The frequency of the C allele in *CFH* Y402H was 14.3% and 16.7%, respectively, in the patients with and without reticular pseudodrusen (Table 6). The 2×2 table from the allele χ^2 test revealed no C allele contribution to reticular pseudodrusen ($P = .845$).

In contrast, the A69S polymorphism in the *ARMS2* gene apparently contributed to reticular pseudodrusen (Table 6). The frequency of homozygosity for the at-risk genotype (TT) of A69S was 60.7% and 38.4%, respectively, in patients with and without reticular pseudodrusen. Furthermore, the frequency of the T allele in A69S was 78.6% and 59.9%, respectively. When examined with a 2×2 table from the allele χ^2 test, we found the T allele contributed significantly to reticular pseudodrusen ($P = .007$).

DISCUSSION

RETICULAR PSEUDODRUSEN HAS TRADITIONALLY BEEN identified with blue-light fundus photography. However, with the development of various imaging modalities, recent studies have suggested that additional methods such as FAF, IR imaging, and SD OCT would facilitate the identification of reticular pseudodrusen.[4,5,7,9,10,13,14] In all these cited studies, multiple imaging modalities were used to detect reticular pseudodrusen, with diagnosis based on the least positive modality. However, the reticular pattern is sometimes subtle and difficult to distinguish from other alterations (soft/hard drusen) when using only 1 imaging modality (Figure 2). Therefore, we used 4 imaging methods. Reticular pseudodrusen-affected eyes were defined as those with reticular patterns discovered with the use of >2 imaging modalities. Among these 4 modalities, IR showed the highest sensitivity for detecting reticular pseudodrusen, consistent with previous studies.[9,14]

Previous reports suggest that IA is also useful for detecting reticular pseudodrusen.[14,27,28] Here, we reviewed IA images from patients with reticular pseudodrusen. In many eyes, hyporeflective dots were detected in the

TABLE 4. Characteristics of Patients Without Reticular Pseudodrusen in Late Age-Related Macular Degeneration

	Typical AMD	PCV	RAP	Geographic Atrophy	Combined[a]	Total
No. of patients	88	85	2	6	5	186
Sex, n (%)						
Men	71 (81)	70 (82)	1 (50)	5 (83)	3 (60)	150 (81)
Women	17 (19)	15 (18)	1 (50)	1 (17)	2 (40)	36 (19)
No. of eyes with AMD (%)						
Two	14 (16)	9 (11)	1 (50)	3 (50)	5 (100)	32 (17)
One	74 (84)	76 (89)	1 (50)	3 (50)		154 (83)
Age (mean ± SD)	74.2 ± 8.3	71.3 ± 8.4	76.0 ± 11.3	66.2 ± 6.2	81.8 ± 3.3	72.8 ± 8.5

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; SD = standard deviation.

[a]Patients with typical AMD, PCV, RAP, or geographic atrophy in 1 eye and another type of AMD in the other eye (1 RAP and geographic atrophy, 1 AMD and RAP, and 1 AMD and PCV).

TABLE 5. Prevalence of Reticular Pseudodrusen in Each Disease Type of Late Age-Related Macular Degeneration

	No. of Patients	No. of Patients With Reticular Pseudodrusen	Prevalence (%)
Typical AMD	97	9	9.2
PCV	87	2	2.2
RAP	12	10	83.3
Geographic atrophy	12	6	50.0
Combined[a]	8	3	37.5

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation.

[a]Patients with typical AMD, PCV, RAP, or geographic atrophy in 1 eye and another type of AMD in the other eye (4 typical AMD and PCV, 1 typical AMD and RAP, 1 typical AMD and geographic atrophy, 1 geographic atrophy and RAP, and 1 geographic atrophy and PCV).

middle and late phases of reticular pseudodrusen development. These dots correspond to the reticular pattern detected in IR and FAF. Smith and associates reported that IA detected reticular pseudodrusen with 100% sensitivity, although the sample size was small.[14] Our findings suggest that IA is a useful method to detect reticular pseudodrusen.

In our study, the proportion of women was higher in the reticular pseudodrusen group than in the group without reticular pseudodrusen. Patients with reticular pseudodrusen were older than those without. These results are consistent with previous reports indicating that women and older patients are more likely to have reticular pseudodrusen.[3,4,10,14] In addition, many reticular pseudodrusen patients in our study had bilateral late AMD. Arnold and associates reported that CNV was found in 66 of 100 patients with reticular pseudodrusen; bilateral CNV was found in 24 patients.[3] Pumariega and associates showed that reticular pseudodrusen was associated with progression to late AMD in the fellow eye.[6] Thus, ophthalmologists should be aware that patients with reticular pseudodrusen have the risk of bilateral late AMD and should conduct follow-ups on these patients.

The prevalence of reticular pseudodrusen has been described in several reports. A population-based study revealed that the overall prevalence was 0.7% in the general population. The associated 15-year incidence increased from 0.4% to 6.6% with age, which is similar to the trend observed for AMD.[8] In AMD patients, the prevalence of reticular pseudodrusen ranged from 9% to 36%.[3,4,10,13] In the current study, reticular pseudodrusen was detected in 14% of patients with late AMD. This small number may be explained by the following reasons: the diagnosis of reticular pseudodrusen was based on reticular patterns as observed in ≥2 imaging modalities; our cohort included many patients with PCV, in whom reticular pseudodrusen was rarely detected; our subjects were younger (mean age, 73.9 years) than the subjects studied by Cohen and associates (mean age, 79.5 years) [4]; and our study had relatively fewer women than those in previous reports, although the sex distribution was similar to that of other Japanese AMD studies.[29] Considering that women are more likely than men to have reticular pseudodrusen, sex distribution may be one of the reasons for low prevalence of reticular pseudodrusen. Reticular pseudodrusen may fade with post-CNV development.[14] Smith and associates included only the fellow eyes of patients with unilateral CNV.[13] The current study included patients with bilateral CNV; some of these patients may have had reticular pseudodrusen before CNV development. We speculate that there may be ethnic differences in the reticular pseudodrusen prevalence between Japanese and white populations, similar to the varying prevalence of soft drusen among AMD patients.[30-32] A recent Korean study indicated that ethnic differences may be associated with certain clinical features.[33]

TABLE 6. Distribution of Genotype of ARMS2 A69S, CFH I62 V, and CFH Y402 in Patients With vs Without Reticular Pseudodrusen in Late Age-Related Macular Degeneration

	Reticular Pseudodrusen (+) (n=28)					Reticular Pseudodrusen (-) (n=177)					
	Genotype, n (%)			Allele, n (%)		Genotype, n (%)			Allele, n (%)		P[a]
ARMS2 A69S	GG	GT	TT	G	T	GG	GT	TT	G	T	
	1 (3.6)	10 (35.7)	17 (60.7)	12 (21.4)	44 (78.6)	33 (18.7)	76 (42.9)	68 (38.4)	142 (40.1)	212 (59.9)	.007
CFH I62 V	AA	AG	GG	A	G	AA	AG	GG	A	G	
	4 (14.3)	4 (14.3)	20 (71.4)	12 (21.4)	44 (78.6)	16 (9.1)	49 (27.8)	111 (63.1)	81 (23.0)	271 (77.0)	.865
CFH Y402	CC	CT	TT	C	T	CC	CT	TT	C	T	
	1 (3.6)	6 (21.4)	21 (75.0)	8 (14.3)	48 (85.7)	7 (4.0)	45 (25.4)	125 (70.6)	59 (16.7)	295 (83.3)	.845

[a]P value with 2 × 2 table of allele χ^2 test for its exact counterpart.

In the current study, reticular pseudodrusen prevalence was high in eyes with RAP or geographic atrophy, consistent with previous reports.[5,6] Therefore, reticular pseudodrusen may represent a hallmark or adverse effect associated with the pathology of RAP and geographic atrophy. In contrast, reticular pseudodrusen was rarely found in PCV patients (2%). To our knowledge, this is the first report on reticular pseudodrusen prevalence in PCV patients.

Literature suggests an association between AMD and polymorphisms in the *CFH* gene.[15-19,24] The Y402H and I62 V variants, in particular, have been specifically reported to be associated with AMD.[15-19,24] In a Japanese cohort, we have previously shown that both *CFH* Y402H and I62 V are associated with AMD.[19] The Beaver Dam Eye Study showed a higher prevalence of reticular pseudodrusen in participants carrying the Y402H mutation of the C allele, which is associated with an increased risk of AMD.[8] In contrast, Smith and associates reported that this *CFH* variant was significantly associated with absence of reticular pseudodrusen.[25] We found no association between reticular pseudodrusen and *CFH* Y402H in patients with late AMD. As the frequency of the Y402H C allele is very low in the Asian population,[34-36] it may be difficult to show a significant difference. In contrast, I62 V is more suitable for an association study focusing on the *CFH* gene in Japanese people, because its minor allele frequency is approximately 40%.[19,24] However, in the current study, we found no association between I62 V and reticular pseudodrusen.

The A69S variant of the *ARMS2* gene is also associated with AMD; this association was reported in white and Asian subjects.[19-23,37-42] Smith and associates reported that the *ARMS2* A69S allele increases the risk for reticular pseudodrusen.[25] In the current study, the T-allele frequencies of the *ARMS2* A69S were higher in reticular pseudodrusen patients, which suggests that the A69S polymorphism contributed to reticular pseudodrusen development. Although we reported higher T-allele frequencies for *ARMS2* A69S than Smith and associates,[25] the risk-allele frequency in patients without reticular pseudodrusen was similar to that reported in previous studies on Japanese patients.[43,44] The finding that both the *ARMS2* risk allele and reticular pseudodrusen apparently lead to late AMD may suggest a common mechanism. Although the function of *ARMS2* is unknown, Fritsche and associates showed that *ARMS2* was expressed in the ellipsoid region of the photoreceptor inner segments.[39] Despite the controversial localization of reticular pseudodrusen, several researchers have shown that reticular pseudodrusen location corresponds to that of abnormal material above the RPE.[9,45] Thus, *ARMS2* expression may colocalize with reticular pseudodrusen, raising the possibility that *ARMS2* may play a role in the formation of reticular pseudodrusen. Meanwhile, other reports suggest that the reticular pattern is related to impaired choroidal filling, as observed in our subjects, and may involve the RPE, choriocapillaris, and inner choroid.[3,14,46] Querques and associates proposed that derangement of the RPE attributable to underlying atrophy and fibrosis of the choroid might lead to the accumulation of photoreceptor outer segments above the RPE.[28] Kertvely and associates showed that *ARMS2* gene expression localized primarily to the intercapillary area of the choroid.[47] Further investigations are required on the histology of reticular pseudodrusen and the locations and functions of *ARMS2* during the course of AMD.

Our study had several limitations. First, this study was retrospective, and the imaging protocol was not standardized. Second, the sample size was relatively small compared with that used in other prevalence and genetic studies, and we included several disease types. Third, a single grader subjectively evaluated image quality. When the same researcher evaluated it again, intra-observer agreement was high. Fourth, our results show that the prevalence of reticular pseudodrusen was high in patients with RAP or geographic atrophy, but the small sample size of these patients prevented us from establishing this trend. Finally, the techniques used here may have failed to identify reticular pseudodrusen in eyes in which reticular pseudodrusen was present only on the nasal side of the optic disc.[13] Furthermore, some patients with

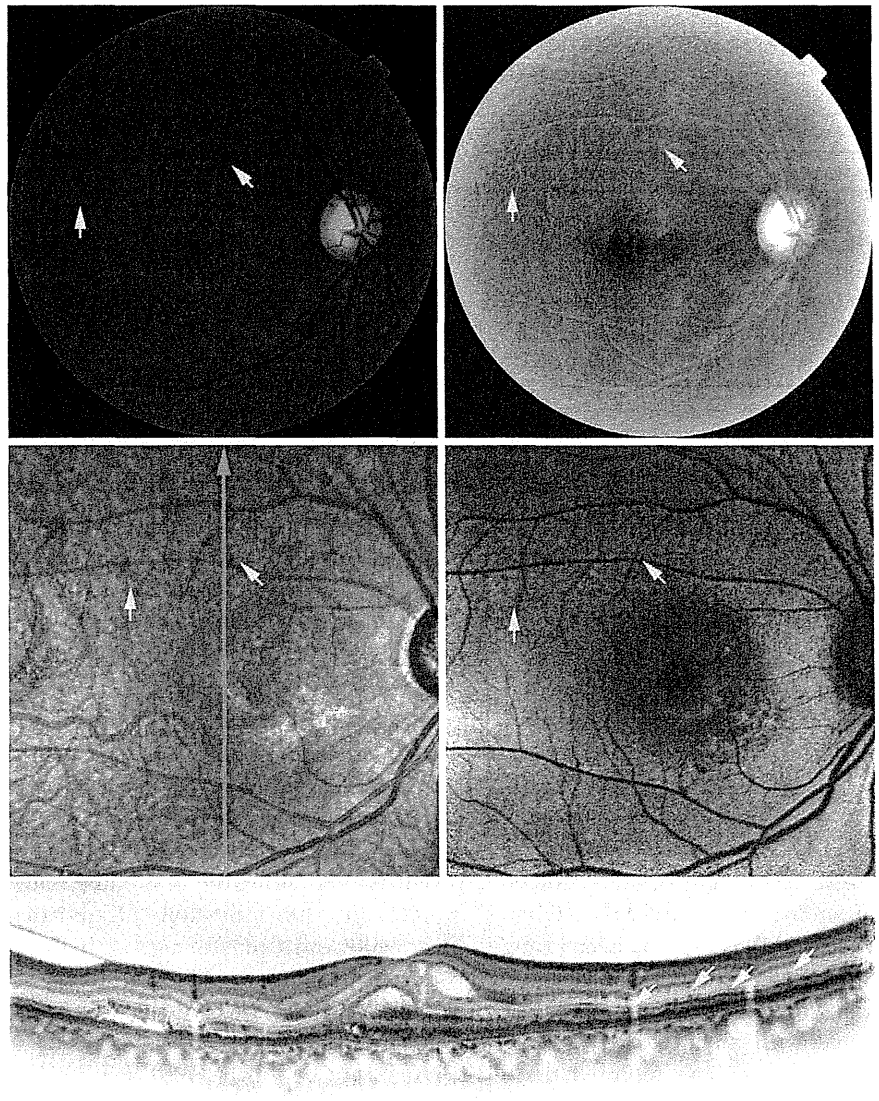

FIGURE 2. Images of a patient with neovascular age-related macular degeneration and reticular pseudodrusen. (Top row, left) Color fundus photography. (Top row, right) Blue channel of contrast-enhanced color fundus photography. (Second row, left) Infrared reflectance imaging. (Second row, right) Fundus autofluorescence imaging. (Bottom) Spectral-domain optical coherence tomography (vertical B-scan thorough the fovea in the direction of the green arrow in Second row, left). Reticular pattern is visible in each imaging (arrows), but it may be difficult to make a diagnosis of reticular pseudodrusen using only 1 imaging method.

bilateral CNV may have had reticular pseudodrusen before CNV development.

In conclusion, reticular pseudodrusen was found in 14% of patients with newly diagnosed late AMD using multimodal imaging. About half of the patients with reticular pseudodrusen had bilateral late AMD. Moreover, there was an association between reticular pseudodrusen and the *ARMS2* gene. Further epidemiologic or genetic studies will deepen our understanding of the clinical significance of reticular pseudodrusen.

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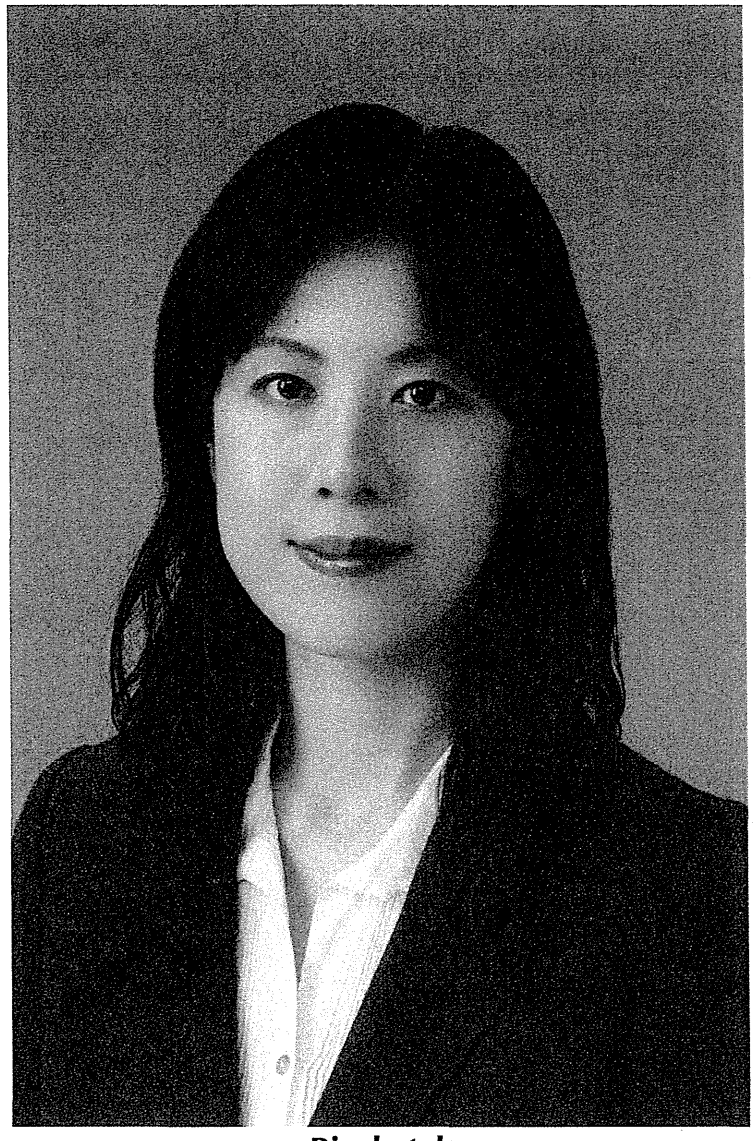
REFERENCES

1. Mimoun G, Soubrane G, Coscas G. Les drusen maculaires. *J Fr Ophtalmol* 1990;13(10):511–530.
2. Klein R, Davis MD, Magli YL, et al. The Wisconsin age-related maculopathy grading system. *Ophthalmology* 1991; 98(7):1128–1134.
3. Arnold JJ, Sarks SH, Killingsworth MC, et al. Reticular pseudodrusen. A risk factor in age-related maculopathy. *Retina* 1995;15(3):183–191.
4. Cohen SY, Dubois L, Tadayoni R, et al. Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularization. *Br J Ophthalmol* 2007;91(3):354–359.
5. Sarks J, Arnold J, Ho I-V, Sarks S, Killingsworth M. Evolution of reticular pseudodrusen. *Br J Ophthalmol* 2011;95(7):979–985.
6. Pumariega NM, Smith RT, Sohrab MA, LeTien V, Souied EH. A prospective study of reticular macular disease. *Ophthalmology* 2011;118(8):1619–1625.
7. Schmitz-Valckenberg S, Alten F, Steinberg JS, et al. Reticular drusen associated with geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2011;52(9):5009–5015.
8. Klein R, Meuer SM, Knudtson MD, Iyengar SK, Klein BEK. The epidemiology of retinal reticular drusen. *Am J Ophthalmol* 2008;145(2):317–326.
9. Zweifel SA, Spaide RF, Curcio CA, et al. Reticular pseudodrusen are subretinal drusenoid deposits. *Ophthalmology* 2010;117(2):303–312.
10. Zweifel SA, Imaura Y, Spaide TC, Fujiwara T, Spaide RF. Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. *Ophthalmology* 2010;117(9):1775–1781.
11. Lois N, Owens SL, Coco R, Hopkins J, Fitzke FW, Bird AC. Fundus autofluorescence in patients with age-related macular degeneration and high risk of visual loss. *Am J Ophthalmol* 2002;133(3):341–349.
12. Bindewald A, Bird AC, Dandekar SS, et al. Classification of fundus autofluorescence patterns in early age-related macular disease. *Invest Ophthalmol Vis Sci* 2005;46(9):3309–3314.
13. Smith RT, Chan JK, Busuoic M, et al. Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2006; 47(12):5495–5504.
14. Smith RT, Sohrab MA, Busuioc M, Barile G. Reticular macular disease. *Am J Ophthalmol* 2009;148(5):733–743.
15. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *PNAS* 2005;102(20):7227–7232.
16. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science* 2005; 308(5720):385–389.
17. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science* 2005;308(5720):419–421.
18. Edwards AO, Ritter R 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. *Science* 2005; 308(5720):421–424.
19. Hayashi H, Yamashiro K, Gotoh N, et al. CFH and ARMS2 variations in age-related macular degeneration, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation. *Invest Ophthalmol Vis Sci* 2010;51(11):5914–5919.
20. Schmidt S, Hauser MA, Scott WK, et al. Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. *Am J Hum Genet* 2006;78(5): 852–864.
21. Dewan A, Liu M, Hartman S, et al. HTRA1 promoter polymorphism in wet age-related macular degeneration. *Science* 2006;314(5801):989–992.
22. Yang Z, Camp NJ, Sun H, et al. A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. *Science* 2006;314(5801):992–993.
23. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Hum Mol Genet* 2005;14(21):3227–3236.
24. Mori K, Horie-Inoue K, Gehlbach PL, et al. Phenotype and genotype characteristics of age-related macular degeneration in a Japanese population. *Ophthalmology* 2010;117(5):928–938.
25. Smith RT, Merriam JE, Sohrab MA, et al. Complement factor H 402H variant and reticular macular disease. *Arch Ophthalmol* 2011;129(8):1061–1066.
26. Yannuzzi LA, Negrao S, Iida T, et al. Retinal angiomatous proliferation in age-related macular degeneration. *Retina* 2001;21(5):416–434.
27. Arnold JJ, Quaranta M, Soubrane G, Sarks SH, Coscas G. Indocyanine green angiography of drusen. *Am J Ophthalmol* 1997;124(3):344–356.
28. Querques G, Querques L, Forte R, Massamba N, Coscas F, Souied EH. Choroidal changes associated with reticular pseudodrusen. *Invest Ophthalmol Vis Sci* 2012;53(3):1258–1263.
29. Maruko I, Iida T, Saito M, Nagayama D, Saito K. Clinical characteristics of exudative age-related macular degeneration in Japanese patients. *Am J Ophthalmol* 2007;144(1):15–22.
30. Oshima Y, Ishibashi T, Murata T, Tahara Y, Kiyohara Y, Kubota T. Prevalence of age-related maculopathy in a retrospective Japanese population: the Hisayama study. *Br J Ophthalmol* 2001;85(10):1153–1157.
31. Klein R, Chou CF, Klein BE, Zhang X, Meuer SM, Saaddine JB. Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol* 2011;129(1):75–80.
32. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 1992;99(6):933–943.
33. Lee MY, Yoon J, Ham DI. Clinical characteristics of reticular pseudodrusen in Korean patients. *Am J Ophthalmol* 2012; 153(3):530–535.
34. Gotoh N, Yamada R, Hiratani H, et al. No association between complement factor H gene polymorphism and exudative age-related macular degeneration in Japanese. *Hum Genet* 2006;120(1):139–143.
35. Fuse N, Miyazawa A, Mengkegale M, et al. Polymorphisms in Complement Factor H and Hemicentin-1 genes in a Japanese population with dry-type age-related macular degeneration. *Am J Ophthalmol* 2006;142(6):1074–1076.
36. Kim NR, Kang JH, Kwon OW, Lee SJ, Oh JH, Chin HS. Association between complement factor H gene polymorphisms

and neovascular age-related macular degeneration in Koreans. *Invest Ophthalmol Vis Sci* 2008;49(5):2071–2076.
37. Kondo N, Honda S, Ishibashi K, Tsukahara Y, Negi A. LOC387715/HTRA1 variants in polypoidal choroidal vasculopathy and age-related macular degeneration in a Japanese population. *Am J Ophthalmol* 2007;144(4):608–612.
38. Magnusson KP, Duan S, Sigurdsson H, et al. *CFH* Y402H confers similar risk of soft drusen and both forms of late AMD. *PLoS Med* 2006;3(1):e5.
39. Fritsche LG, Loenhardt T, Janssen A, et al. Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA. *Nat Genet* 2008;40(7):892–896.
40. Deangelis MM, Ji F, Adams S, et al. Alleles in the HtrA serine peptidase 1 gene alter the risk of neovascular age-related macular degeneration. *Ophthalmology* 2008;115(7):1209–1215.e7.
41. Sakurada Y, Kubota T, Mabuchi F, Imasawa M, Tanabe N, Iijima H. Association of LOC387715 A69S with vitreous hemorrhage in polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2008;145(6):1058–1062.
42. Lee KY, Vithana EN, Mathur R, et al. Association analysis of CFH, C2, BF, and HTRA1 gene polymorphisms in Chinese patients with polypoidal choroidal vasculopathy. *Invest Ophthalmol Vis Sci* 2008;49(6):2613–2619.
43. Gotoh N, Nakanishi H, Hayashi H, et al. ARMS2 (LOC387715) variants in Japanese patients with exudative age-related macular degeneration and polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2009;147(6): 1037–1041.
44. Yanagisawa S, Kondo N, Miki A, et al. Difference between age-related macular degeneration and polypoidal choroidal vasculopathy in the hereditary contribution of the A69S variant of the age-related maculopathy susceptibility 2 gene (ARMS2). *Mol Vis* 2011;17:3574–3582.
45. Schmitz-Valckenberg S, Steinberg JS, Fleckenstein M, Visvalingam S, Brinkmann CK, Holtz FG. Combined confocal scanning laser ophthalmoscopy and spectral-domain optical coherence tomography imaging of reticular drusen associated with age-related macular degeneration. *Ophthalmology* 2010;117(6):1169–1176.
46. Sohrab MA, Smith RT, Salehi-Had H, Sadda SR, Fawzi AA. Image registration and multimodal imaging of reticular pseudodrusen. *Invest Ophthalmol Vis Sci* 2011;52(8):5743–5748.
47. Kertvely E, Hauck SM, Duetsch G, et al. ARMS2 is a constituent of the extracellular matrix providing a link between familial and sporadic age-related macular degenerations. *Invest Ophthalmol Vis Sci* 2010;51(1):79–88.



Biosketch

Naoko Ueda-Arakawa, MD, graduated from Kyoto University, Faculty of Medicine. She completed her residency program at Kyoto University Hospital and a fellowship at Osaka Red Cross Hospital, Osaka, Japan. She is now in a PhD program in the Department of Ophthalmology and Visual Sciences at Kyoto University under the supervisor of Professor Nagahisa Yoshimura. Her main interest is imaging analysis of macular diseases.

SUPPLEMENTAL TABLE. Prevalence of Reticular Pseudodrusen in Patients Over 70 Years of Age

	No. of Patients	No. of Patients With Reticular Pseudodrusen	Prevalence (%)
Typical AMD	67	8	11.9
PCV	53	2	3.8
RAP	11	10	90.9
Geographic atrophy	7	5	71.4
Combined[a]	8	3	37.5

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation.

[a]Patients with typical AMD, PCV, RAP, or geographic atrophy in 1 eye and another type of AMD in the other eye (4 typical AMD and PCV, 1 typical AMD and RAP, 1 typical AMD and geographic atrophy, 1 geographic atrophy and RAP, and 1 geographic atrophy and PCV).

Factors Associated With the Response of Age-Related Macular Degeneration to Intravitreal Ranibizumab Treatment

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• PURPOSE: To investigate factors affecting patient response to intravitreal ranibizumab treatment for age-related macular degeneration (AMD).
• DESIGN: Retrospective chart review.
• METHODS: We reviewed medical records of 105 consecutive eyes with AMD treated with intravitreal ranibizumab injections and followed for more than 1 year after treatment. Response to ranibizumab treatment was compared between typical neovascular AMD and polypoidal choroidal vasculopathy (PCV). Furthermore, we investigated associations of age, lesion size, and single nucleotide polymorphisms (SNPs) in *CFH* and *ARMS2* genes with treatment response.
• RESULTS: Forty-nine eyes were diagnosed with typical neovascular AMD and 56 eyes with PCV. Serous retinal detachment and retinal edema resolved similarly in both typical neovascular AMD and PCV after treatment. However, visual acuity (VA) significantly improved in eyes with PCV, whereas VA was maintained in typical neovascular AMD. At the third and twelfth months after injection, VA was better in PCV than in typical neovascular AMD ($P = .027$ and $P = .044$, respectively), although there were no differences in baseline VA between the 2 groups. Age and size of greatest linear dimension were significantly associated with visual prognosis in typical neovascular AMD but not in PCV. There was no clear association between 3 SNPs and responsiveness to ranibizumab treatment.
• CONCLUSIONS: Although exudative changes were equivalent following ranibizumab treatment in both typical neovascular AMD and PCV, there was a significant increase in VA in PCV compared to typical neovascular AMD. Age and greatest linear dimension correlated with visual prognosis only in typical neovascular AMD and not in PCV. (Am J Ophthalmol 2012;154:125–136.

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AGE-RELATED MACULAR DEGENERATION (AMD) IS the leading cause of severe visual impairment in industrialized countries in people over 50 years of age. However, anti–vascular endothelial growth factor (VEGF) treatment, such as bevacizumab or ranibizumab, has dramatically improved visual prognosis in patients suffering from neovascular AMD. After numerous reports of favorable results following anti-VEGF treatment for neovascular AMD, anti-VEGF treatment has been extended to treat eyes with polypoidal choroidal vasculopathy (PCV), a subtype of neovascular AMD. Although some reports show that PCV is refractory to anti-VEGF treatment,[1,2] recent studies have demonstrated improvements in visual acuity (VA) after anti-VEGF treatment for PCV.[3–8]

Recently, increasing numbers of studies have compared the characteristics of PCV and typical AMD.[9–14] Maruko and associates demonstrated that Japanese patients with neovascular AMD could be further characterized into subtypes including PCV (54.7%), typical neovascular AMD (35.3%), retinal angiomatous proliferation (4.5%), and PCV + typical neovascular AMD (5.5%).[9] They included predominantly classic choroidal neovascularization (CNV), minimally classic CNV, and occult with no classic CNV into typical neovascular AMD. It has been reported that there is greater VA improvement in PCV compared to typical neovascular AMD after photodynamic therapy (PDT).[10] Furthermore, we have previously shown that there are significant differences in the genetic associations involved in the development of typical neovascular AMD and PCV.[11] For instance, the *ARMS2* gene is more strongly related to typical neovascular AMD development than PCV, whereas there is no significant difference in the association of the *CFH* gene with typical neovascular AMD or PCV.

In addition to disease development, recent studies have examined genetic associations with various treatments for AMD and PCV; several studies have shown a significant association between *ARMS2/HTRA1* and visual outcome in eyes with AMD and PCV after PDT, whereas a definitive association with *CFH* could not be found.[14–16] The association of the aforementioned genes with response to ranibizumab treatment is still controversial. In addition

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TABLE 1. Demographics, Retinal Exudative Change, and Visual Acuity of the Neovascular Age-Related Macular Degeneration Patients Treated With Intravitreal Ranibizumab

	Typical Neovascular AMD	PCV	*P*
Number of eyes	49	56	
Age (years)	75.9 ± 8.8	74.2 ± 8.6	NS
Sex (male/female)	34/15	41/15	NS
Baseline retinal exudative change			
GLD (μm)	4490.4 ± 273.9	3988.1 ± 322.6	NS
Retinal edema	71.2%	50.0%	.025
SRD	69.3%	73.2%	NS
Disappearance of retinal exudative change			
3 months	65.3%	62.5%	NS
12 months	69.4%	55.3%	NS
Visual acuity (logMAR)			
Baseline	0.56 ± 0.42	0.48 ± 0.41	NS
3 months	0.57 ± 0.48	0.38 ± 0.37[a]	.027
12 months	0.60 ± 0.53	0.40 ± 0.47[b]	.044

AMD = age-related macular degeneration; GLD = greatest linear dimension; NS = not significant; PCV = polypoidal choroidal vasculopathy; SRD = serous retinal detachment.
[a] $P < .01$ compared with baseline.
[b] $P < .05$ compared with baseline.

to genetic associations, baseline VA, CNV lesion size, and age are important predictors of VA outcomes after ranibizumab treatment for AMD.[17,18] However, it is not clear if these factors are associated with VA outcomes after ranibizumab treatment for PCV.

In the present study, we aimed to elucidate predictive factors of response to ranibizumab in neovascular AMD. At first, we compared response to ranibizumab treatment between typical neovascular AMD and PCV. Furthermore, we evaluated the correlation of baseline VA, age, and lesion size to VA outcome after ranibizumab treatment in typical neovascular AMD and PCV patients. In addition, we investigated the association of 3 major AMD-susceptibility single nucleotide polymorphisms (SNPs) in the *CFH* (Y402H, I62V) and *ARMS2* (A69S) genes and attempted to correlate their presence with response to ranibizumab treatment.

METHODS

WE RETROSPECTIVELY REVIEWED THE MEDICAL RECORDS OF 105 eyes from 105 consecutive patients with subfoveal neovascular AMD. All patients were treated with 3 loading intravitreal injections of 0.5 mg ranibizumab (Lucentis; Novartis, Bülach, Switzerland) at 1-month intervals and were followed up for more than 12 months after the initial treatment at Kyoto University Hospital. Before treatment, all patients underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (VA), intraocular pressure testing, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, spectral-domain optical coherence tomography (OCT) (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), and fluorescein and indocyanine green angiography (HRA-2; Heidelberg Engineering). Best-corrected VA was measured using a Landolt chart and converted to a logarithm of the minimal angle of resolution (logMAR) for statistical analysis. The diagnosis of PCV was based on indocyanine green angiography, which revealed a branching vascular network terminating in polypoidal swellings. Typical AMD involved classic CNV, occult CNV, or a combination of both. Greatest linear dimension was also determined by indocyanine green angiography.

Ranibizumab injections were administered in a sterile manner, and prophylactic topical antibiotics were applied regularly for 1 week after the injection. After the 3 loading injections, patients were followed up every month, and retreatments were performed as required when VA declined more than 0.2 logMAR along with signs of exudation on OCT or angiography, when retinal thickness increased greater than 100 μm, or if subretinal fluid, subretinal hemorrhage, or active CNV persisted or developed. Photodynamic therapy (PDT) was administered to some eyes whose retinal edema or subretinal fluid did not decrease after initial ranibizumab treatment; we judged that those eyes were resistant to ranibizumab.

Genotyping was performed in 78 patients. Genomic DNA was prepared from patients' peripheral blood using a DNA extraction kit (QuickGene-610L; Fujifilm, Minato, Tokyo, Japan). *CFH* Y402H rs1061170, I62V rs800292, and *ARMS2* A69S rs10490924 were genotyped using the

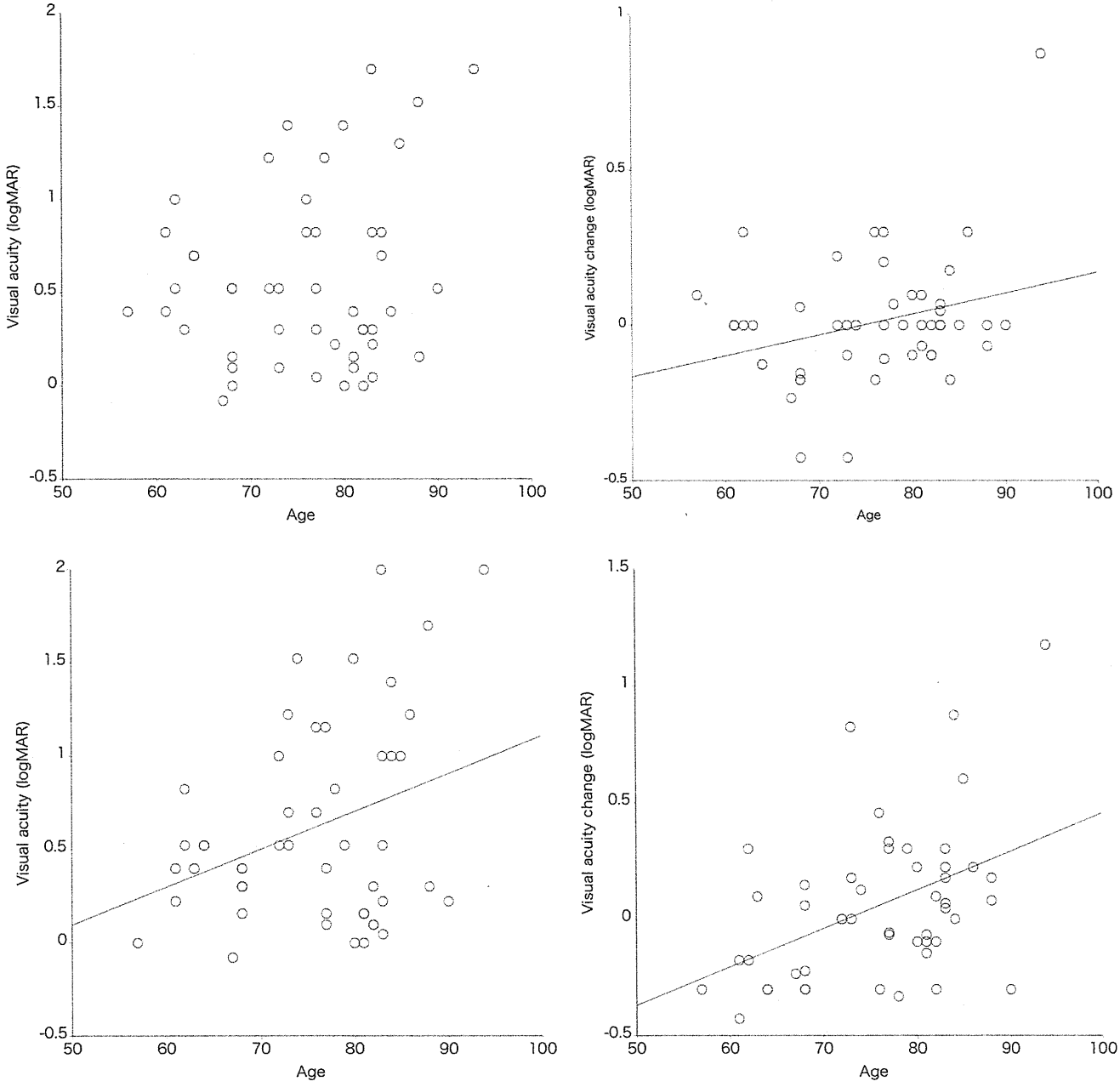

FIGURE 1. Relationship between visual prognosis after ranibizumab treatment and the age of patients with typical neovascular age-related macular degeneration. Visual acuity is expressed as a logarithm of the minimal angle of resolution (logMAR). Although there is no statistically significant correlation between visual acuity (VA) at 3 months and patient age ($P = .18$, Top left), age was significantly correlated with VA change at 3 months ($P = .040$, Top right), VA at 12 months ($P = .020$, Bottom left), and VA change at 12 months ($P = .0014$, Bottom right).

Taqman SNP assay with the ABI PRISM 7700 system (Applied Biosystems, Foster City, California, USA).

All values are presented as mean ± standard deviation. Patient age, baseline greatest linear dimension, and visual acuity at baseline, 3 months, and 12 months were compared using unpaired *t* test between typical neovascular AMD and PCV. Sex ratio, baseline existence rate of retinal edema and serous retinal detachment, and disappearance rate of retinal exudative change during follow-up were compared using χ^2 test between typical neovascular AMD and PCV. Visual acuity change during follow-up was evaluated using a paired *t* test. Associations of baseline visual acuity, patient age, and greatest linear dimension to visual acuity at 3 months and 12 months and visual acuity change during follow-up were evaluated with the Pearson correlation test. Associations of genotypes to visual acuity at 3 months and 12 months and visual acuity change during follow-up were evaluated with analysis of variance

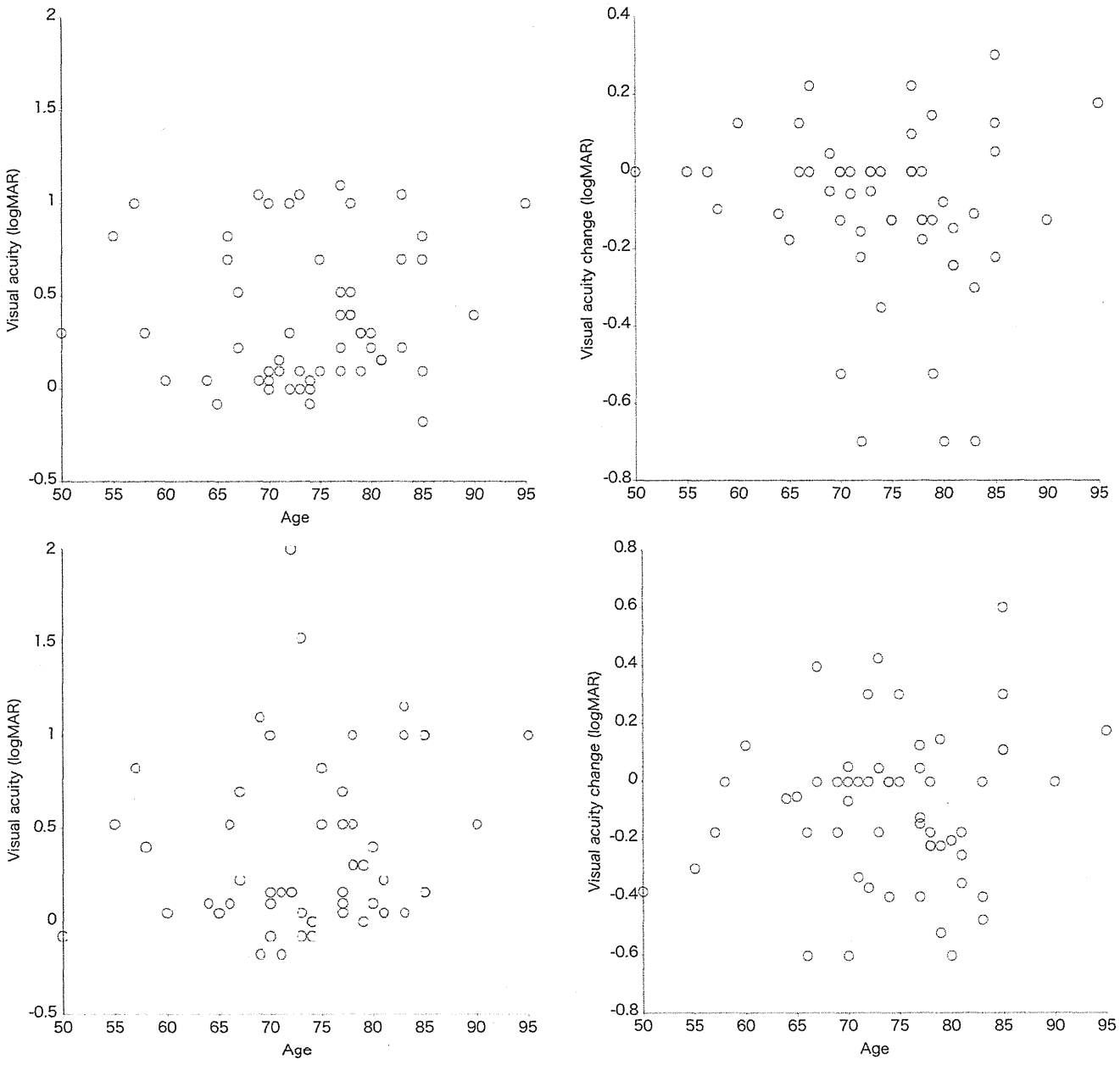

FIGURE 2. Relationship between visual prognosis after ranibizumab treatment and the age of patients with polypoidal choroidal vasculopathy. Patient age did not significantly correlate with VA at 3 months (P = .76, Top left), VA change at 3 months (P = .37, Top right), VA at 12 months (P = .22, Bottom left), or VA change at 12 months (P = .32, Bottom right).

and post hoc comparisons of Scheffe's procedure, and associations to disappearance of retinal exudative change at 3 months and 12 months were evaluated with χ^2 test for trend. *P* values of less than .05 were considered statistically significant.

RESULTS

DEMOGRAPHICS OF THE STUDY POPULATION ARE SHOWN in Table 1. Of the 105 eyes evaluated, 49 had typical neovascular AMD and 56 had PCV. Mean age was not significantly different between the 2 groups. All eyes presented with an exudative change attributable to AMD: retinal edema was seen in 35 of 49 eyes (71.4%) with typical neovascular AMD and in 28 of 56 eyes (50%) with PCV and serous retinal detachment was seen in 34 of 49 eyes (69.4%) with typical neovascular AMD and 41 of 56 eyes (73.2%) with PCV. All exudative features revealed by OCT resolved in 32 of 49 eyes (65.3%) with typical neovascular AMD and 35 of 56 eyes (62.5%) with PCV at the third month, and in 34 of 49 eyes (69.4%) with typical neovascular AMD and 31 of 56 eyes (55.4%) with PCV at the twelfth month. There were no significant differences

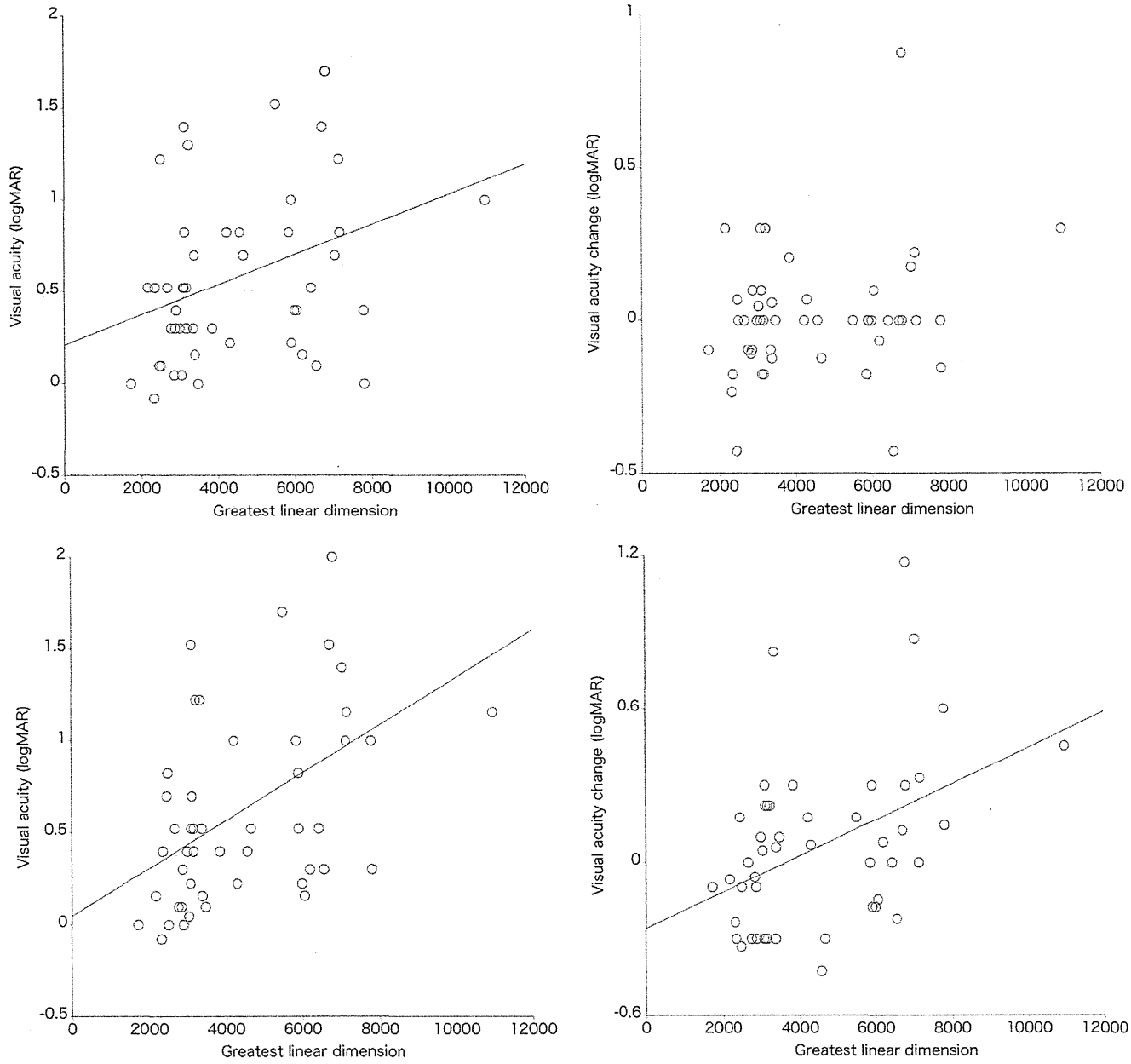

FIGURE 3. Relationship between visual prognosis after ranibizumab treatment and the greatest linear dimension size in typical neovascular age-related macular degeneration. Although there is no statistically significant correlation between VA change at 3 months and the greatest linear dimension size (P = .12, Top right), age significantly correlated with VA at 3 months (P = .015, Top left), VA at 12 months (P = .0004, Bottom left), or VA change at 12 months (P = .0021, Bottom right).

between typical neovascular AMD and PCV with respect to the effectiveness of ranibizumab to resolve retinal exudative change ($P = .77$ and $P = .14$, respectively).

Although there were no differences in baseline VA between typical neovascular AMD and PCV ($P = .29$), VAs were better in PCV than in AMD at the third and twelfth months ($P = .027$ and $P = .044$, respectively). So we compared VA change between typical neovascular AMD and PCV. In eyes with PCV, after the first treatment, VA significantly improved at the third month ($P = .002$) and at the twelfth month ($P = .028$), whereas in typical neovascular AMD, VA was stable at the third month ($P = .79$) and at the twelfth month ($P = .23$).

Twelve eyes with typical neovascular AMD and 15 eyes with PCV had been previously treated with anti-VEGF therapy, and 2 eyes with typical neovascular AMD and 7 eyes with PCV had been previously treated with PDT. After the 3 loading injections, an average of 1.37 ± 1.52 and 1.70 ± 1.88 injections were added to the treatment of patients with typical neovascular AMD and PCV, respectively, during the 1-year follow-up period. There was no significant difference in the frequency of additional treat-

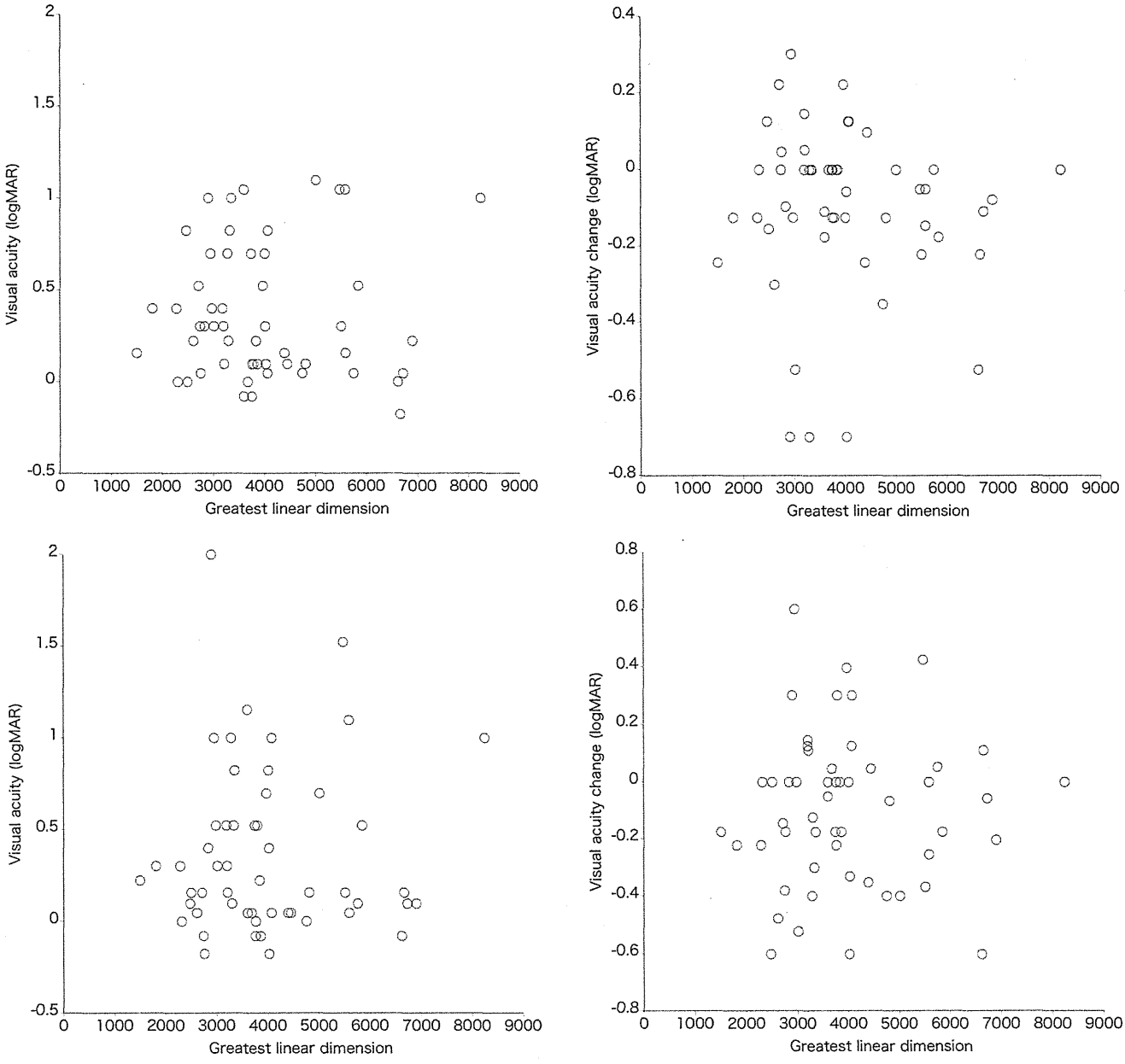

FIGURE 4. Relationship between visual prognosis after ranibizumab treatment and the greatest linear dimension size of polypoidal choroidal vasculopathy. The greatest linear dimension size did not significantly correlate with VA at 3 months (P = .90, Top left), VA change at 3 months (P = .63, Top right), VA at 12 months (P = .70, Bottom left), or VA change at 12 months (P = .93, Bottom right).

ments between the 2 groups ($P = .33$). Seven of 49 eyes (14.3%) with typical neovascular AMD and 8 of 56 eyes (14.3%) with PCV were treated with PDT after the initial treatment because ranibizumab treatment did not decrease the retinal edema or subretinal fluid. The number of eyes resistant to ranibizumab treatment was not significantly different between patients with typical neovascular AMD or PCV ($P > .99$). In the 7 typical neovascular AMD eyes and the 8 PCV eyes treated with PDT, the average VA did not significantly change at the third month ($P = .96$ and $P = .27$, respectively) and the twelfth month ($P = .55$ and $P = .60$, respectively). VA declined more than 0.2 logMAR in 1 or 2 eyes with typical neovascular AMD and PCV at the third month and twelfth month, while VA remained unchanged in most eyes.

Since the MARINA[17] and ANCHOR studies[18] have shown that important predictors of VA outcomes in AMD after ranibizumab treatment are baseline VA, CNV lesion size, and patient age, we evaluated the correlations of baseline VA, CNV lesion size, and patient age to the visual prognosis. The Pearson correlation test revealed significant correlation between baseline VA and the VA at the third