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Association between the SERPING1 Gene and Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy in Japanese

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Abstract

Purpose: Recently, a complement component 1 inhibitor (*SERPING1*) gene polymorphism was identified as a novel risk factor for age-related macular degeneration (AMD) in Caucasians. We aimed to investigate whether variations in *SERPING1* are associated with typical AMD or with polypoidal choroidal vasculopathy (PCV) in a Japanese population.

Methods: We performed a case-control study in a group of Japanese patients with typical AMD (n = 401) or PCV (n = 510) and in 2 independent control groups—336 cataract patients without age-related maculopathy and 1,194 healthy Japanese individuals. Differences in the observed genotypic distribution between the case and control groups were tested using chi-square test for trend. Age and gender were adjusted using logistic regression analysis.

Results: We targeted rs2511989 as the haplotype-tagging single nucleotide polymorphism (SNP) for the *SERPING1* gene, which was reported to be associated with the risk of AMD in Caucasians. Although we compared the genotypic distributions of rs2511989 in typical AMD and PCV patients against 2 independent control groups (cataract patients and healthy Japanese individuals), *SERPING1* rs2511989 was not significantly associated with typical AMD (P = 0.932 and 0.513, respectively) or PCV (P = 0.505 and 0.141, respectively). After correction for age and gender differences based on a logistic regression model, the difference in genotypic distributions remained insignificant (P > 0.05). Our sample size had a statistical power of more than 90% to detect an association of a risk allele with an odds ratio reported in the original studies for rs2511989 for developing AMD.

Conclusions: In the present study, we could not replicate the reported association between *SERPING1* and either neovascular AMD or PCV in a Japanese population; thus, the results suggest that *SERPING1* does not play a significant role in the risk of developing AMD or PCV in Japanese.

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Introduction

Age-related macular degeneration (AMD) is the leading cause of visual loss in the developed world [1]. Several genes have been reported to be associated with this disease, including complement factor H [2–4] and the age-related maculopathy susceptibility 2/HtrA serine peptidase 1 (ARMS2/HTRA1) region [5,6], and subsequent studies have replicated the association between susceptibility genes and the development of AMD using a different ethnic cohort [7–10].

Inner choroidal vascular networks that terminate in polypoidal lesions are defined as polypoidal choroidal vasculopathy (PCV), and are typically visualized by indocyanine green angiography [11]. Whether PCV represents a subtype of neovascular AMD remains controversial; moreover, whether this condition represents inner choroidal vascular abnormalities or is a variety of choroidal neovascularization remains unknown [12]. Previous studies identified several genes that contribute to the development of PCV; however, almost all reported genetic risk factors for PCV are the same as for AMD [13–15], and this suggests that AMD and PCV share, at least in part, the same genetic background.

Studies in cohorts from both the United Kingdom and the United States have shown that the complement component 1 inhibitor (*SERPING1*) gene is positively associated with AMD [16]. However,

Table 1. Characteristics of the Study Population.

		Cases		Controls	
		tAMD	PCV	Control 1*	Control 2†
No. of participants		401	510	336	1194
Age	Mean ± SD	77.38±8.39	74.98±7.77	74.16±8.42	50.34±15.9
Gender	Men	287	372	142	493
	Women	114	138	194	701

tAMD, typical age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; SD, standard deviation.
*Cataract patients without age-related maculopathy.
†Healthy Japanese individuals.
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another study in a larger cohort (n = 7723 and 2327) which involved the same population could not replicate the finding of the previous study [17,18]. Recently, Lee et al. have shown that *SERPING1* is positively associated with AMD in Caucasians [19], but whether this gene is truly associated with AMD remains controversial.

Furthermore, the association of *SERPING1* with AMD has been evaluated also in Asians. Lu et al. examined the association in 194 AMD patients and 285 controls and reported that *SERPING1* is not associated with AMD in the Chinese population [20]. The association between PCV and *SERPING1* has also been evaluated in a smaller Chinese cohort (118 patients and 115 controls), also with negative findings [21]. So far, all Asian studies for *SERPING1* did use smaller cohorts than those of original studies and not consider their statistical power. For evaluating the true gene-disease association, it would be helpful to replicate the positive association reported in previous studies using a different ethnic cohort. The aim of this study, which involved a relatively large number of participants, was to investigate whether the *SERPING1* gene variants are associated with typical AMD or PCV in a Japanese population.

Materials and Methods

All procedures in this study adhered to the tenets of the Declaration of Helsinki. This study was approved by the Ethics Committee of each institute involved (Kyoto University Graduate School and Faculty of Medicine, Ethics Committee, the Ethical

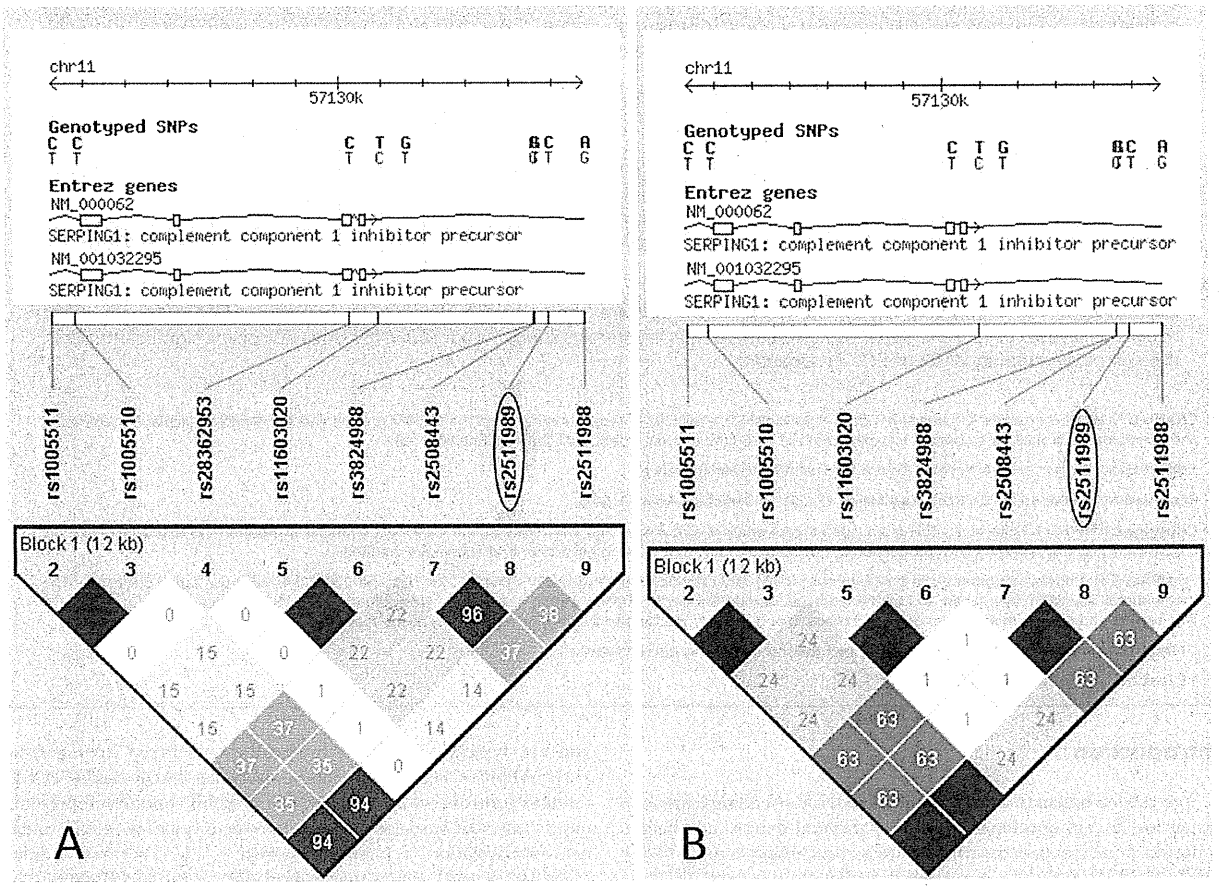

Figure 1. Linkage disequilibrium (LD) structure across the complement component 1 inhibitor (*SERPING1*) gene in Caucasian and Japanese populations. Genotype data were retrieved from HapMap CEU (Utah residents with ancestry from northern and western Europe; A) and JPT (Japanese in Tokyo, Japan; B) data sets. Haplotype blocks were determined using the "four-gamete rule" option in Haploview; all HapMap single nucleotide polymorphisms on *SERPING1* gene are in the same block in both populations. Each box provides estimated statistics of the coefficient of determination (r^2), with darker shades representing stronger LD.
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Committee of Fukushima Medical University, the Ethical Committee of Kobe City Medical Center General Hospital, the Ethical Committee of Ozaki Eye Hospital, the Ethical Committee of the Otsu Red Cross Hospital, the Ethical Committee of Nagahama City Hospital, and the Ethical Committee at Aichi Cancer Center). All of the patients were fully informed about the purpose and procedures of this study, and written consent was obtained from each.

In this study, 401 patients with typical AMD and 510 patients with PCV were recruited from the Department of Ophthalmology at Kyoto University Hospital, Fukushima Medical University Hospital, and Kobe City Medical Center General Hospital. The control group included 2 populations: (1) 336 individuals who underwent cataract surgery and had no age-related maculopathy (ARM) (Control 1) were recruited from the Department of Ophthalmology, Kyoto University Hospital, Ozaki Eye Hospital, Japanese Red Cross Otsu Hospital, and Nagahama City Hospital; and (2) 1194 healthy individuals who were recruited from the Aichi Cancer Center Research Institute as the general population control (Control 2). AMD and ARM were defined according to the International Classification System for ARM and AMD [22]. The diagnosis of PCV was based on indocyanine green angiography, which showed a branching vascular network that terminated in polypoidal swelling. Typical AMD were late AMD which showed classic choroidal neovascularization (CNV), occult CNV, or both. All diagnoses were made by 3 retina specialists (K.Y., A.T., and A.O.); a fourth specialist (N.Y.) was consulted when the subtype classification could not be decided on by the initial 3 reviewers. All of the subjects were unrelated and were of the Japanese descent.

Genomic DNAs were isolated from the peripheral blood of the subjects by using a DNA extraction kit (QuickGene-610L, Fujifilm, Minato, Tokyo, Japan). The samples of all the patients with typical AMD and PCV and of cataract patients were genotyped using a Taqman single nucleotide polymorphism (SNP) assay with the ABI PRISM 7700 system (Applied Biosystems, Foster City, CA). The individuals recruited from the Aichi Cancer Center Research Institute were genotyped using Illumina Human-Hap 610 chips (Illumina Inc., San Diego, CA).

Linkage disequilibrium (LD) structures across the *SERPING1* gene were compared between the Caucasian and Japanese populations, using genotype data retrieved from the HapMap CEU and JPT data sets [23]. The retrieved data were loaded into Haploview to estimate LD parameters and to identify haplotype blocks [24]. Deviations in genotype distributions from the Hardy–Weinberg equilibrium (HWE) were assessed using the HWE exact test. Statistical analyses for differences in the observed genotypic distribution were performed by the chi square test for trend; logistic regression analysis was performed for age and gender adjustments. The statistical power calculation was performed using QUANTO version 1.2 [25]. P values less than 0.05 were considered statistically significant.

Results

The demographic details of the study population are presented in Table 1. Because all SNPs of the *SERPING1* gene are in the same haplotype block, rs2511989 was selected as the haplotype-tagging SNP; rs2511989 was reported to be associated with the risk of AMD in previous studies [16,19] (Fig. 1). Details of allele and genotype counts and summary statistics for rs2511989 are shown in Table 2. The success rate of genotyping of rs2511989 was 98.1%, and the distributions of the genotypes for all study groups were in the Hardy–Weinberg equilibrium ($P>0.05$). Although we compared the genotype distributions of rs2511989 in typical AMD and PCV patients against 2 independent control groups (cataract patients without ARM and healthy Japanese individuals), *SERPING1* rs2511989 was not significantly associated with typical AMD ($P=0.932$ and 0.513, respectively); furthermore, it was not significantly associated with PCV ($P=0.505$ and 0.141, respectively). After correction for age and gender differences based on a logistic regression model, the difference in the genotype distributions remained insignificant ($P>0.05$). Table 3 shows the odds ratios adjusted for age and gender under various genetic models. We could not find a significant association in any genetic model.

Next, we calculated our statistical power to detect an association of a risk allele with the odds ratio reported in the previous study that investigated the association of rs2511989 with developing AMD. When we targeted the original study reported by Ennis (odds ratio 0.63) [16], our sample size had more than 90% power to detect the association (Table 2). In addition, the statistical power calculation revealed that our sample size could detect the gene-disease association for an odds ratio of 0.797 by more than 80%.

Discussion

In the present study, we investigated whether *SERPING1* gene variants are associated with typical AMD or with PCV in a Japanese population. We selected rs2511989 as the haplotype-tagging SNP, because this has been reported to be positively associated with the risk of AMD in Caucasians. The results of this study showed that *SERPING1* rs2511989 was not associated with the risk for typical AMD in a Japanese population; thus, the results did not support the hypothesis that an association between the *SERPING1* gene and AMD exists. Our sample size had more than 90% power to detect the association determined in the previous

Table 2. *SERPING1* rs2511989 Genotypic Distributions and Results of Association Tests and Power Analysis.

						vs Control 1			vs Control 2		
		GG	GA	AA	MAF	P Value	Adjusted P*	Power†	P Value	Adjusted P*	Power†
Cases	tAMD	293	102	6	0.142	0.932	0.687	93.6%	0.513	0.860	99.3%
	PCV	380	125	5	0.132	0.505	0.855	95.7%	0.141	0.678	99.2%
Controls	Control 1	248	76	10	0.144	-	-	-	-	-	-
	Control 2	859	308	27	0.152	-	-	-	-	-	-

tAMD, typical age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; MAF, minor allele frequency.
*Adjusted for age and gender.
†Statistical power for detecting the association reported in the previous study (odds ratio 0.63).
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Table 3. Odds Ratios in Various Genetic Models.

Group	Model	Adjusted Odds Ratio (95% Confidence Interval)*	
		vs tAMD	vs PCV
Control 1	Additive	0.938 (0.687–1.281)	0.972 (0.72–1.312)
	Dominant	1.283 (0.746–2.204)	0.598 (0.338–1.056)
	Recessive	0.934 (0.783–1.114)	1.283 (0.746–2.204)
Control 2	Additive	1.034 (0.716–1.491)	0.933 (0.673–1.294)
	Dominant	0.940 (0.470–1.879)	0.709 (0.349–1.440)
	Recessive	1.025 (0.839–1.254)	0.983 (0.823–1.174)

*Adjusted for age and gender.
tAMD, typical age-related macular degeneration; PCV, polypoidal choroidal vasculopathy.
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study in a Caucasian cohort (odds ratio 0.63) [16]. Furthermore, we found no evidence to support the role played by *SERPING1* rs2511989 in the susceptibility to PCV, and this finding is in agreement with that of the previous study in a Chinese population [21].

The reported association between AMD and *SERPING1* rs2511989 is shown in Table 4. The size of our Japanese cohort was similar to that of the original study [16]. Furthermore, the statistical power calculation revealed that our sample size could detect the gene-disease association for an odds ratio of 0.797 by more than 80%. Had there been a true protective effect of *SERPING1* gene variants for developing AMD at the same level as was reported in previous studies [16,19], the statistical power of our study would have detected such an association. Differences in the ethnicities of subjects might be 1 reason for the difference observed between the results of this study in a Japanese cohort and those of the previous study in a Caucasian cohort. Frequency of the minor allele of rs2511989 was reportedly greater in the earlier study in a Caucasian population than that of the present study in a Japanese population. In fact, in reference to the allele frequency data from the HapMap, all genetic variants across the *SERPING1* gene showed smaller minor allele frequency in Japanese than in Caucasians.

Another possible explanation for the differences between our findings and those of other studies in different ethnic cohorts may include a difference in the phenotypes of AMD. Numerous studies have reported that distinguishing features of Asian AMD include male predominance, unilateral presentation, comparatively low incidence of soft drusen, and greater prevalence of neovascular AMD and PCV [26–29]. To address these concerns, we classified AMD patients into those with typical AMD and those with PCV, but the possible hidden differences in the phenotypes cannot be excluded. Alternatively, considering the fact that genetic variants that are associated with a particular disease in 1 population may not necessarily be associated in another population [30–32]; moreover, it is possible that gene-disease association of *SERPING1* in populations from East Asia is very weak or absent as compared with Caucasian populations.

In this study, we used general population-based controls (Control 2). The possibility exists that some of the eyes in the control 2 group might have or develop AMD or PCV, and this might be a possible explanation for the negative results in this study. However, because the prevalence of AMD in the general population is estimated to be 0.5% in the Japanese population [33], the loss of the statistical power of association analysis must be negligible. In addition, we also performed a subset analysis on

Table 4. Comparison of Association Observed between AMD and *SERPING1* rs2511989.

Subject Group		Current Study (JP)			Mayo Subjects (US)		AREDS Subjects (US)		Ennis et al. (UK)		Ennis et al. (US)		Lee et al. (US)		Lu et al. (CH)	
Subjects		Case	Control 1	Control 2	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
No. of participants		401	336	1194	470	310	1221	295	479	479	248	252	556	256	194	285
Allele count	G	688	572	2026	569	363	1435	357	597	500	322	282	669	283	336	493
	A	114	96	362	371	257	1007	233	355	454	174	222	413	229	52	69
Genotype count	GG	293	248	859	179	103	436	115	191	132	100	79	213	74	147	215
	GA	102	76	308	211	157	563	127	215	236	122	124	273	135	42	63
	AA	6	10	27	80	50	222	53	70	109	26	49	70	47	5	3
MAF		0.142	0.144	0.152	0.395	0.415	0.412	0.395	0.373	0.475	0.351	0.441	0.382	0.447	0.134	0.123
P values		-	0.932	0.513	-	0.46	-	0.41	-	5.4×10^{-6}	-	0.0037	-	0.011	-	0.61

MAF, minor allele frequency.
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controls 2 with 55 years of age or older to minimize the possibility that some of the eyes in the control group might develop AMD or PCV. However, no new significant differences in the genotypic distributions were found in the current study (data not shown). Thus, we concluded that the result of the analysis using control 2 is valuable as reference data which supports a lack of association between *SERPING1* and both typical AMD and PCV in a Japanese population. Another limitation is about geographical difference of Control 1, which may influence genetic background of the participants. However, because the Japanese population has been reported to have a rather small genetic diversity, according to data from the SNP discovery project in Japan [34], geographical difference should not be affect our statistical results.

In conclusion, this study showed a lack of association between *SERPING1* and both typical AMD and PCV in a Japanese population; thus, the results suggest that *SERPING1* does not play a significant role in the risk of developing AMD or PCV in Japanese.

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Author Contributions

Conceived and designed the experiments: IN KY HN NY. Performed the experiments: IN NG HN HH. Analyzed the data: IN RY. Contributed reagents/materials/analysis tools: IN KY RY NG HN HH AT AO MS TI AO KM KT FM NY. Wrote the paper: IN KY RY.

Association of Lesion Size and Visual Prognosis to Polypoidal Choroidal Vasculopathy

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• PURPOSE: To investigate the progression of vascular lesions of polypoidal choroidal vasculopathy (PCV) as viewed with indocyanine green angiography and the visual prognosis of these eyes.

• DESIGN: Retrospective case study.

• METHODS: We reviewed retrospectively the medical records of 88 consecutive patients (88 eyes) with PCV who had been examined with indocyanine green angiography for more than 2 years.

• RESULTS: Depending on the initial area of the vascular lesion, eyes were divided into smaller PCV (baseline area of lesion being < 1 disc area [DA], n = 22) and larger PCV (baseline area of lesion being ≥ 1 DA, n = 66). In larger PCV, the mean area of the lesion progressed significantly from 6.49 ± 8.96 mm^2 to 16.27 ± 14.19 mm^2 ($P < .0001$) with marked deterioration of visual acuity ($P < .0001$) during follow-up. In contrast, smaller PCV often showed minimal progression of the lesion, only limited exudative change, and the eyes maintained their initially good vision to the final visit. Smaller PCV lesions rarely progressed to extensive PCV lesions. Severe vision-threatening complications (ie, suprachoroidal hemorrhage, vitreous hemorrhage, and tears of the retinal pigment epithelium) were seen only in eyes with larger PCV, and in studying single nucleotide polymorphisms A69S of *ARMS2* genes, there was a significant difference in T allele frequency between individuals with smaller PCV and those with larger PCV (20.2% vs 79.8%; $P = .0235$).

• CONCLUSIONS: PCV with small vascular lesions shows minimal progression and no vision-threatening complications, and these eyes often maintain good visual acuity for a long time. (Am J Ophthalmol 2011;151: 961–972. © 2011 by Elsevier Inc. All rights reserved.)

POLYPOIDAL CHOROIDAL VASCULOPATHY (PCV) first was described as a new clinical entity with a unique form of choroidal vascular abnormality[1–3] and is characterized by a branching vascular network that terminates in polypoidal lesions seen by indocyanine green angiography.[4] Initially, vascular components of PCV are reported to be seen predominantly in a peripapillary location,[5] but macular PCV[6,7] and peripheral PCV[5,8] since have been reported. Yannuzzi and associates expanded the clinical spectrum of this disease and established the current understanding of PCV.[9] Today, macular PCV is more common in Asian populations and seems to be the condition most clinically significant.[7,10,11] To date, however, the pathogenesis of PCV is not understood fully, and it is still controversial whether it originates from an abnormality of the inner choroidal vessels or if it is a variant of choroidal neovascularization (CNV).[12]

PCV is accompanied often by recurrent serosanguineous detachments of the retinal pigment epithelium and neurosensory retina, and sometimes results in massive hemorrhagic complications with a sudden loss of vision.[13,14] Although the extent of visual disturbance in PCV varies, it generally is thought that the visual prognosis of PCV is better than that of exudative age-related macular degeneration (AMD).[11,12] In a previous report by Uyama and associates,[11] approximately half of the patients with PCV had a favorable visual outcome (better than 20/30) after being followed-up for more than 2 years. In PCV, other vision-threatening complications, such as type 2 CNV, disciform scar, or cystoid macular edema, are reported to be uncommon.[10,12]

Clinically, the size of the vascular lesions in PCV varies.[15] We sometimes see cases of PCV with a large lesion that show a poor response to the treatment and show progression of the lesion, resulting in poor visual prognosis. Tateiwa and associates reported that PCV with a large vascular network that extends beyond the vascular arcade is not uncommon, so we may speculate that vascular lesions of originally small PCV extend over time and result in these large PCV.[16] Clinically, however, we rarely see this type of progression.[17] PCV cases with a small lesion often show minimal exudative change and no progression of the lesion and can maintain good visual function for a long time.[18] Even with an exudative change, small PCV often show a favorable response to treatment.[19] Okubo and associates reported that a reddish-orange nodule alone, or that multiple reddish-orange nodules with a small subretinal hemorrhage, is a sign of a potentially

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TABLE 1. Characteristics of Patients with Polypoidal Choroidal Vasculopathy

	Total (n = 88)	Smaller Polypoidal Choroidal Vasculopathy (n = 22)	Larger Polypoidal Choroidal Vasculopathy (n = 66)	*P* Value
Gender (women/men)	28/60	8/14	20/46	.5971
Age (yrs)	70.4 ± 7.5	68.2 ± 6.9	70.8 ± 7.7	.3257
Hypertension	38	11	27	.4560
Smoking	14	4	10	.7365
Location of lesions (macular/peripapillary/peripheral)	79/8/1	22/0/0	57/8/1	.1881
Duration of symptoms (mos)	8.0 ± 11.9	7.0 ± 9.5	8.3 ± 12.6	.6484
Initial conditions				
Best-corrected visual acuity (logMAR)	0.37 ± 0.34	0.24 ± 0.29	0.42 ± 0.35	.0383
Area of lesion (mm^2)	7.75 ± 9.78	1.68 ± 0.53	9.79 ± 10.55	.0006
Greatest linear dimension (μm)	3412 ± 1647	1901 ± 464	3915 ± 1591	<.0001
Foveal thickness (μm)	403.5 ± 189.9	377.6 ± 175.4	412.2 ± 195.0	.4628
Thickness of neurosensory retina in the fovea (μm)	196.5 ± 83.8	209.1 ± 98.5	192.4 ± 78.6	.4204
Follow-up period (months)	46.4 ± 8.1	44.5 ± 6.7	47.0 ± 8.4	.2020
Treatment				
Photodynamic therapy	69	16	53	.3055
(Times of treatments)	1.9 ± 1.1	1.5 ± 0.7	2.1 ± 1.2	.0875
Anti-VEGF therapy	40	6	34	.0480
(Times of treatments)	2.9 ± 2.5	3.8 ± 3.7	2.7 ± 2.2	.3155
Pars plana vitrectomy	4	0	4	.2372
Cataract surgery	8	3	5	.2554
Final conditions				
Best-corrected visual acuity (logMAR)	0.62 ± 0.51	0.19 ± 0.33	0.76 ± 0.49	<.0001
Area of lesion (mm^2)	13.24 ± 13.47	4.13 ± 3.59	16.27 ± 14.19	.0002
Greatest linear dimension (μm)	4511 ± 2030	2761 ± 900	5095 ± 1967	<.0001
Foveal thickness (μm)	299.7 ± 189.5	235.3 ± 65.1	321.2 ± 211.7	.0651
Thickness of neurosensory retina in the fovea (μm)	197.1 ± 168.1	153.3 ± 38.4	211.7 ± 191.1	.1597
Changes during follow-up				
Best-corrected visual acuity (logMAR)	0.24 ± 0.51	−0.05 ± 0.36	0.34 ± 0.51	.0015
Area of lesion (mm^2)	5.48 ± 8.13	2.45 ± 3.53	6.49 ± 8.96	.0429
Greatest linear dimension (μm)	1100 ± 1204	860 ± 933	1180 ± 1278	.2838
Foveal thickness (μm)	−103.8 ± 221.9	−142.3 ± 163.6	−91.0 ± 237.8	.3500
Thickness of neurosensory retina in the fovea (μm)	0.6 ± 168.0	−55.8 ± 103.3	19.3 ± 181.4	.0691

logMAR = logarithm of the minimal angle of resolution; VEGF = vascular endothelial growth factor; yrs = years.

One disc area (DA) is estimated as 2.54 mm^2 on the basis of the 1 optic disc diameter of 1.8 mm. Based on the area of lesion at the initial visit, polypoidal choroidal vasculopathy (PCV) eyes were divided into smaller PCV (area of lesion, < 1 DA) and larger PCV (area of lesion, ≥ 1 DA).

benign clinical course, so the clinical course of small and large PCV may be different.[18]

To study the progression of vascular lesions in PCV, it is essential to perform repeated indocyanine green angiography,[4] because most vascular lesions of PCV are located beneath the retinal pigment epithelium.[1–3] So far, however, there is little information on the long-term observation of the vascular components of PCV.[15] In the study described herein, we investigated progression of the vascular lesion of PCV using indocyanine green angiography and visual prognosis of affected eyes. Based on our findings, we report a new classification of PCV and the expected complications and visual prognosis of these 2 types of PCV.

METHODS

FOR THIS OBSERVATIONAL CASE STUDY, WE REVIEWED retrospectively the medical records of 88 consecutive patients (88 eyes) with symptomatic PCV who initially visited the Macula Service of the Department of Ophthalmology at Kyoto University Hospital between Jan-

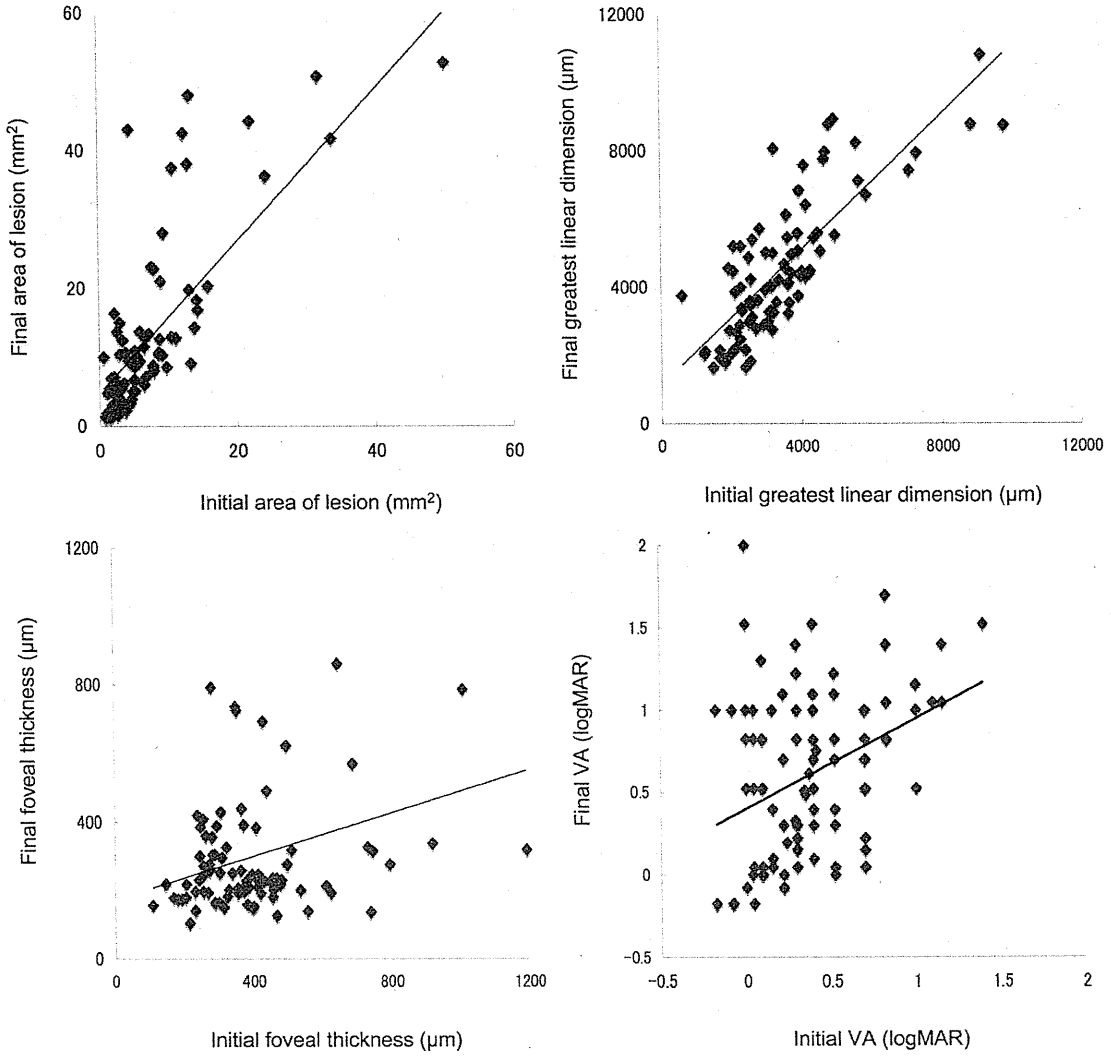

FIGURE 1. Scattergrams showing area of the lesion, greatest linear dimension, foveal thickness, and visual acuity (VA) in eyes with polypoidal choroidal vasculopathy (PCV) obtained at initial and final examinations. (Top left) Initial area is correlated significantly with final area of the lesion ($R = 0.801$; $P < .0001$). (Top right) Initial greatest linear dimension is correlated significantly with final greatest linear dimension ($R = 0.805$; $P < .0001$). (Bottom left) Correlations between initial and final foveal thickness ($R = 0.316$; $P = .0025$) and (Bottom right) initial and final VA ($R = 0.355$, $P = .0006$). VA measured with a Landolt chart was converted to logarithm of the minimal angle of resolution (logMAR) units.

uary 2004 and October 2007 and who had been examined with both fluorescein and indocyanine green angiography for more than 2 years after their initial visit. When both eyes were diagnosed as having PCV, 1 eye was selected randomly for inclusion in the current study.

The diagnosis of PCV was based on indocyanine green angiography, which shows a branching vascular network that terminates in polypoidal swelling. The polypoidal lesion can be a single polyp or a cluster of multiple polyps. In most cases, the reddish-orange nodule that had been seen by the ophthalmoscopic examination corresponded to the polypoidal lesion. Eyes with other macular abnormalities (ie, AMD, pathologic myopia, idiopathic CNV, presumed ocular histoplasmosis, angioid streaks, and other secondary CNV) were excluded from the current study. Eyes that were treated previously with focal laser photocoagulation, photodynamic therapy (PDT), vitrectomy, radiation therapy, or anti–vascular endothelial growth factor (VEGF) therapy also were excluded from the present study.

At the initial visit, all patients underwent a comprehensive ophthalmologic examination, including measurement of best-corrected visual acuity (VA), determination of intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, and optical coherence tomography (OCT). After fundus photographs were obtained, fluorescein and indocyanine green angiography

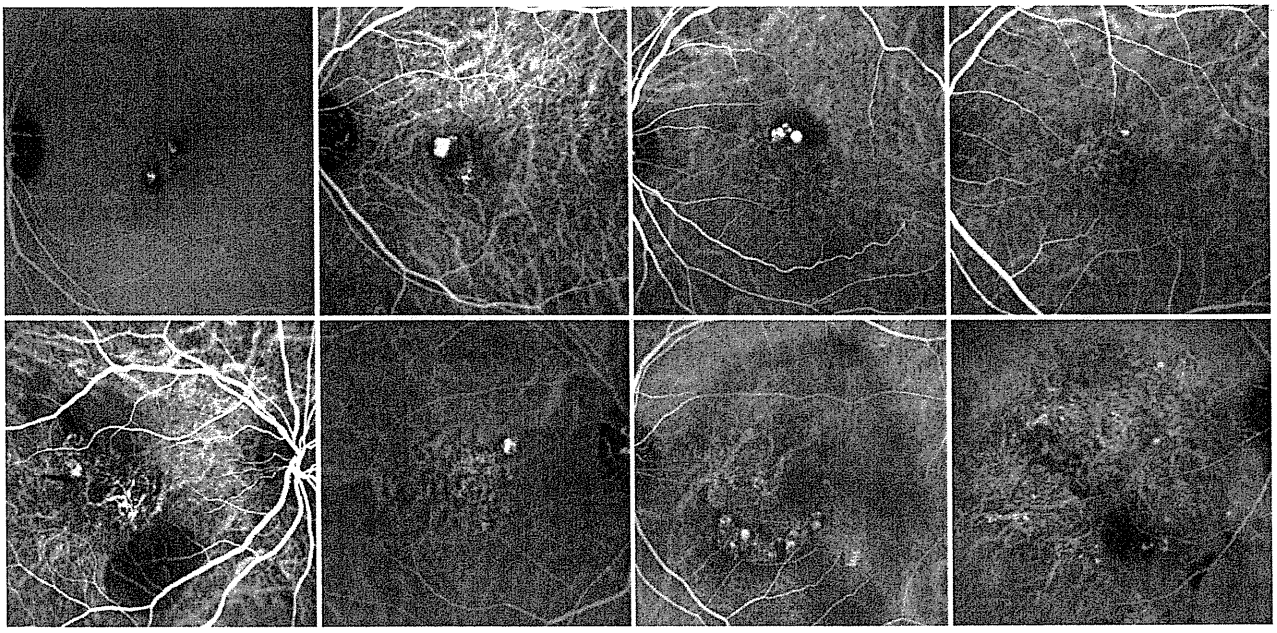

FIGURE 2. Indocyanine green angiograms obtained at the initial visit from eyes with polypoidal choroidal vasculopathy (PCV). All eyes showed the branching vascular network that terminated in a polypoidal lesion, although the lesions varied in size. (Top) Indocyanine green angiograms in the group with smaller PCV. (Bottom) Indocyanine green angiograms in the group with larger PCV.

were performed on each patient using a confocal laser scanning system (HRA-2; Heidelberg Engineering, Dossenheim, Germany). In all patients, VA measurement and OCT examination were performed at each follow-up visit. At follow-up visits, angiography was performed if necessary, although all patients in the current study were examined with angiography several times during follow-up. In the study described herein, the angiograms obtained at the initial visit were compared with the final angiograms.

In the current study, greatest linear dimension and area of the lesion were determined based on the indocyanine green angiography, using the software built into the HRA-2 machine. Greatest linear dimension included the entire PCV vascular lesion, including polypoidal lesion, branching vascular network vessels, and any type 2 CNV. The area of the vascular lesion was measured manually with the software that came with the HRA-2. The pigment epithelial detachment, without underlying vascular components, was not included in measurement of the greatest linear dimension and area of the lesion. In the current study, 1 optic disc area (DA) is equal to 2.54 mm^2, on the basis of 1 optic disc diameter being equal to 1.8 mm. Based on the area of the lesion at the initial visit, we classified the eyes into either the smaller PCV group (baseline area of lesion < 1 DA) or the larger PCV group (baseline area of lesion ≥ 1 DA) to compare the clinical course of the 2 groups.

We also compared the initial OCT measurement and VA with values obtained at the final visit. To compare the difference in VA, VA measured with a Landolt chart was converted to logarithm of the minimal angle of resolution units. Using OCT images, we obtained 2 measurements (foveal thickness and thickness of the neurosensory retina in the fovea) with a caliper that was built into the software of the OCT machine. Foveal thickness was defined as the distance between the vitreoretinal interface and the retinal pigment epithelium; thickness of the neurosensory retina

showing a small protrusion of the retinal pigment epithelium corresponding to the PED. (Second row left) Fluorescein angiogram obtained at the initial visit showing occult choroidal neovascularization corresponding to a branching vascular network. (Second row right) Indocyanine green angiogram revealing large vascular components of PCV consisting of a polypoidal lesion (arrow) and a branching vascular network (long arrow). The area of the PCV lesion was 5.87 mm^2. (Third row left) Despite 3 anti–vascular endothelial growth factor treatments, the vascular lesion progressed. Fundus photograph obtained at 33 months after the initial visit showing a large serosanguineous PED. (Third row right) Sectional image obtained by OCT (with the arrow shown in the fundus photograph) showing a steep protrusion of retinal pigment epithelium, which is reflective of the large PED. (Bottom left) Fluorescein angiogram showing occult choroidal neovascularization corresponding to the branching vascular network. (Bottom right) Indocyanine green angiogram showing progression of the polypoidal lesions and extension of the branching vascular network. The area of the PCV lesion increased to 9.40 mm^2.

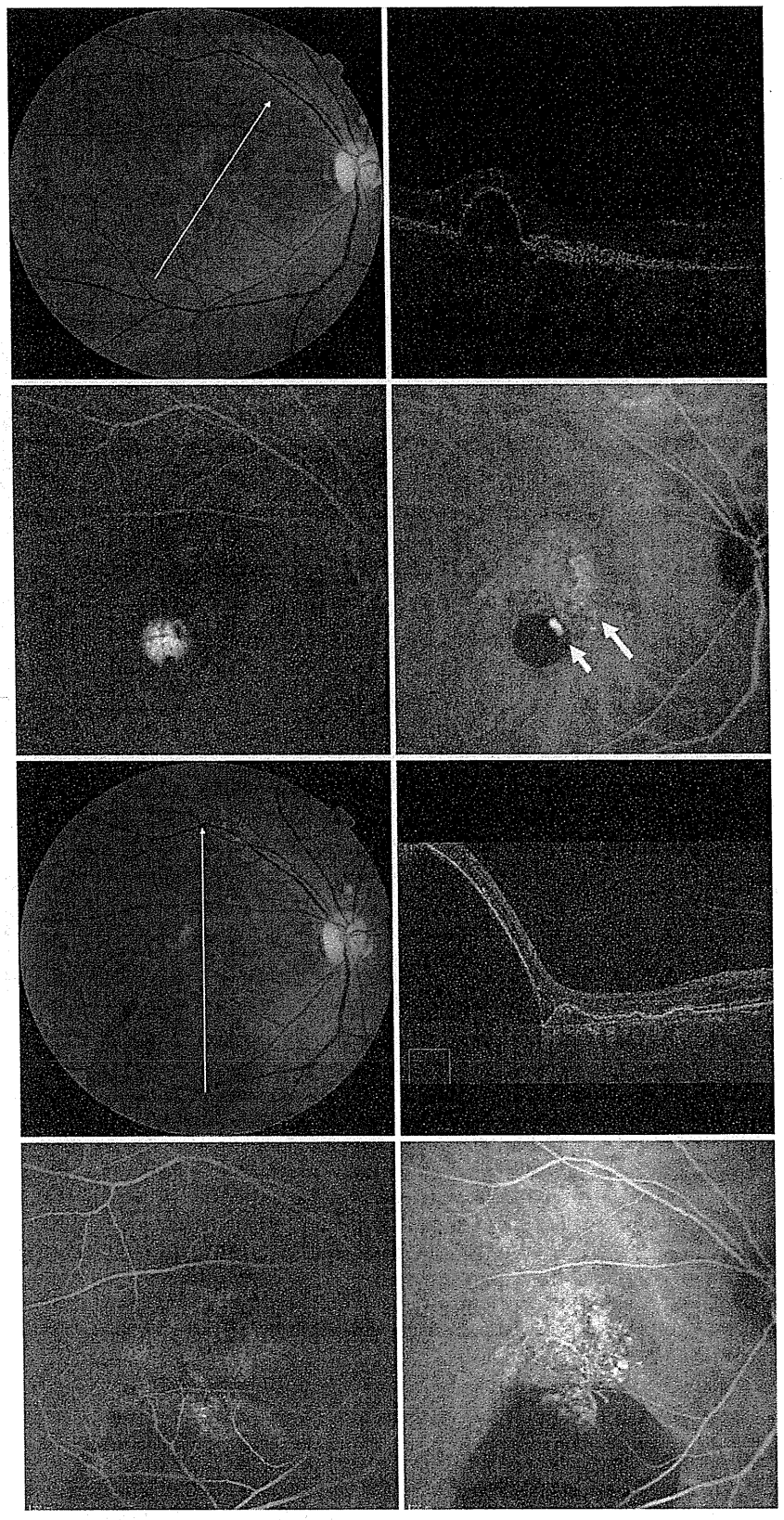

FIGURE 3. Images demonstrating progression of the vascular lesion in larger polypoidal choroidal vasculopathy (PCV). (Top left) Fundus photograph at the initial visit showing a reddish orange nodule with a minute pigment epithelial detachment (PED). (Top right) Sectional image obtained with optical coherence tomography (OCT) along with an arrow seen in the fundus photograph

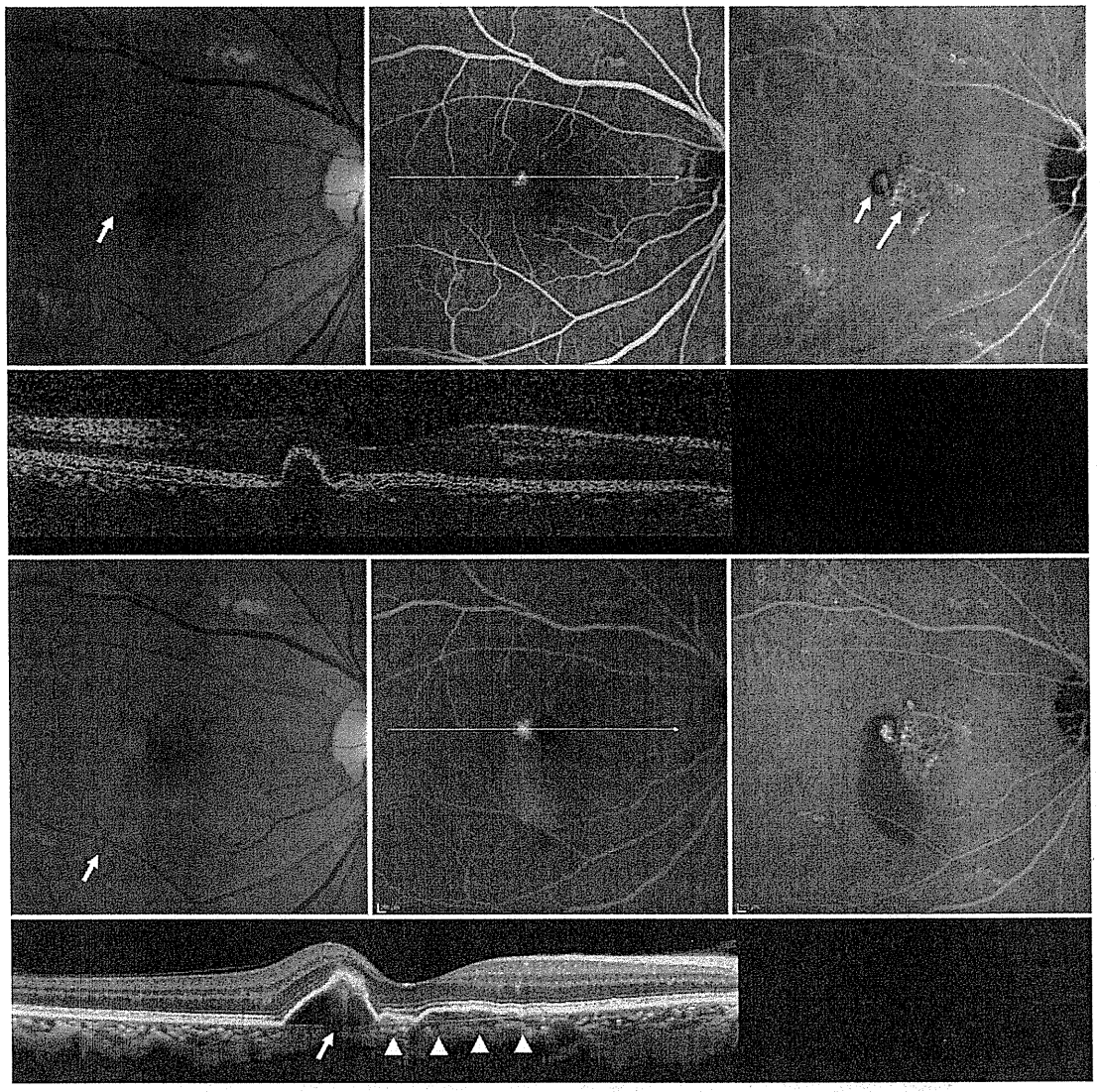

FIGURE 4. Images showing no progression of the vascular lesion in smaller polypoidal choroidal vasculopathy (PCV). (Top left) Fundus photograph at the initial visit showing a small reddish orange nodule (arrow); vision was 20/16. (Top middle) Fluorescein angiogram (FA) obtained at the initial visit showing only a hyperfluorescent spot corresponding to the polypoidal lesion. (Top right) Indocyanine green angiogram showing the vascular components of PCV, which consist of a typical polypoidal lesion (arrow) and a branching vascular network (long arrow). The baseline area of the PCV lesion was 1.77 mm^2. (Second row) Sectional image obtained with optical coherence tomography (OCT) along with the arrow seen in the FA showing a steep protrusion of the retinal pigment epithelium. (Third row left) No treatment was performed. Fundus photograph obtained at 39 months after the initial visit showing a reddish orange nodule with a newly developed serous pigment epithelial detachment; vision was still 20/13. (Third row middle) FA showing a hyperfluorescent spot corresponding to the polypoidal lesion, along with fluorescein pooling in the pigment epithelial detachment. (Third row right) Indocyanine green angiogram revealing no progression of the vascular lesion of PCV. (Bottom) Sectional image obtained with OCT (with the arrow seen on FA) showing protrusion of the retinal pigment epithelium corresponding to the branching network (arrowheads) and steep elevation of the retinal pigment epithelium with moderate inner reflectivity (arrow) corresponding to the polypoidal lesion.

was defined as the distance between the vitreoretinal interface and the tip the outer segment of the inner and outer segments of the photoreceptors.

We genotyped the major AMD- and PCV-associated single nucleotide polymorphism (SNP), rs10490924 (A69S), of *ARMS2*. Genomic deoxyribonucleic acid was prepared from leukocytes of peripheral blood using a deoxyribonucleic acid extraction kit (QuickGene-610L; Fujifilm, Minato, Tokyo, Japan). The SNPs were genotyped using Taqman SNP assays with the ABI PRISM 7700 system (Applied Biosystems, Foster City, California, USA) according to the manufacturer's instructions.

TABLE 2. Ocular Manifestations and Complications Seen in Eyes with Polypoidal Choroidal Vasculopathy during Follow-up

	Total (n = 88)	Smaller Polypoidal Choroidal Vasculopathy (n = 22)	Larger Polypoidal Choroidal Vasculopathy (n = 66)	*P* Value
Suprachoroidal hemorrhage	7	0	7	.1113
Vitreous hemorrhage	8	0	8	.0868
Recurrence	56	11	44	.1620
Type 2 choroidal neovascularization	26	1	25	.0030
Fibrosis	31	4	27	.0533
Serous retinal detachment	81	20	65	.0899
Subretinal hemorrhage (> 1 DA)	55	9	46	.0157
Cystoid macula edema	42	6	36	.0266
Pigment epithelial detachment (> 1 DA)	41	5	36	.0096
Tear of retinal pigment epithelium	8	0	8	.0868

DA = disc area.

One disc area is estimated as 2.54 mm^2 on the basis of 1 optic disc diameter being 1.8 mm. Based on the area of the lesion at the initial visit, polypoidal choroidal vasculopathy (PCV) eyes were divided into smaller PCV (area of lesion, < 1 DA) and larger PCV (area of lesion, ≥ 1 DA).

Statistical analysis was performed using software designed for this purpose (StatView version 5.0; SAS Institute, Cary, North Carolina, USA). A *P* value of less than .05 was considered to be statistically significant.

RESULTS

IN THE CURRENT STUDY, 88 EYES OF 88 PATIENTS (60 MEN and 28 women) with PCV, ranging in age from 50 to 86 years (mean ± standard deviation, 70.4 ± 7.5 years), were examined. The follow-up period ranged from 29 to 61 months (mean ± standard deviation, 46.4 ± 8.6 months), and duration from the initial angiogram to the last ranged from 24 to 60 months (mean ± standard deviation, 39.3 ± 9.4 months). All patients were examined with fluorescein and indocyanine green angiography repeatedly during follow-up, ranging from 2 to 11 times (mean ± standard deviation, 4.9 ± 2.0 times). Table 1 shows the characteristics of patients eligible for inclusion in this study. The mean ± standard deviation baseline VA (logarithm of the minimal angle of resolution) was 0.37 ± 0.34. The mean ± standard deviation initial area of the lesion and greatest linear dimension was 7.75 ± 9.78 mm^2 and 3412 ± 1647 μm, respectively. Figure 1 shows the relationship between area of the lesion, greatest linear dimension, foveal thickness, and VA at initial visit and final examination. Initial area of the lesion (R = 0.801; $P < .0001$) and initial greatest linear dimension (R = 0.805; $P < .0001$) showed a close correlation with final measurements.

PCV vascular lesion at the initial visit varied in size, ranging from 0.64 to 63.82 mm^2. Depending on the initial area of the lesion, we divided the eyes with PCV into 2 groups—the smaller PCV group (baseline area of lesion, < 1 DA; n = 22) and the larger PCV group (baseline area of lesion, ≥ 1 DA; n = 66; Figure 2). The mean area ± standard deviation of the lesion initially was 1.68 ± 0.53 mm^2 in the smaller PCV group and 9.79 ± 10.55 mm^2 in the larger PCV group. There were no significant differences in gender, age, or duration of symptoms between groups (P = .5971, P = .3257, and P = .6484, respectively). In addition, there were no differences in the foveal thickness (P = .4628) or thickness of the neurosensory retina in the fovea (P = .4204) at the initial visit. However, the mean initial VA ± standard deviation was significantly better in eyes with smaller PCV (0.24 ± 0.39) than in eyes with larger PCV (0.42 ± 0.35, P = .0383).

During the follow-up period, 64 eyes were treated initially with PDT, and 9 were treated initially with anti-VEGF therapy. Despite these treatments, some eyes with larger PCV showed extension of the vascular component with an exudative change. The mean area of the lesion ± standard deviation in larger PCV progressed significantly from 9.79 ± 10.55 mm^2 to 16.27 ± 14.19 mm^2 at the final examination ($P < .0001$; Figure 3). Furthermore, mean ± standard deviation VA in these eyes deteriorated significantly 0.42 ± 0.35 to 0.76 ± 0.49 at the final examination ($P < .0001$). In contrast, eyes with smaller PCV lesions often showed minimal progression of the lesion and limited exudative change, and smaller PCV lesions rarely progressed to extensive PCV lesions (Figure 4). However, even in eyes with smaller PCV, the mean lesion size increased during the follow-up period (P = .0037). In smaller PCV, mean ± standard deviation change in the area of the lesion and final area of the lesion were 2.45 ± 3.53 mm^2 and 4.13 ± 3.59 mm^2, respectively, which were significantly less than those of the larger PCV (P = .0429 and P = .0002, respectively). In addition, eyes with the smaller PCV showed no decrease in VA (−0.05 ± 0.36;

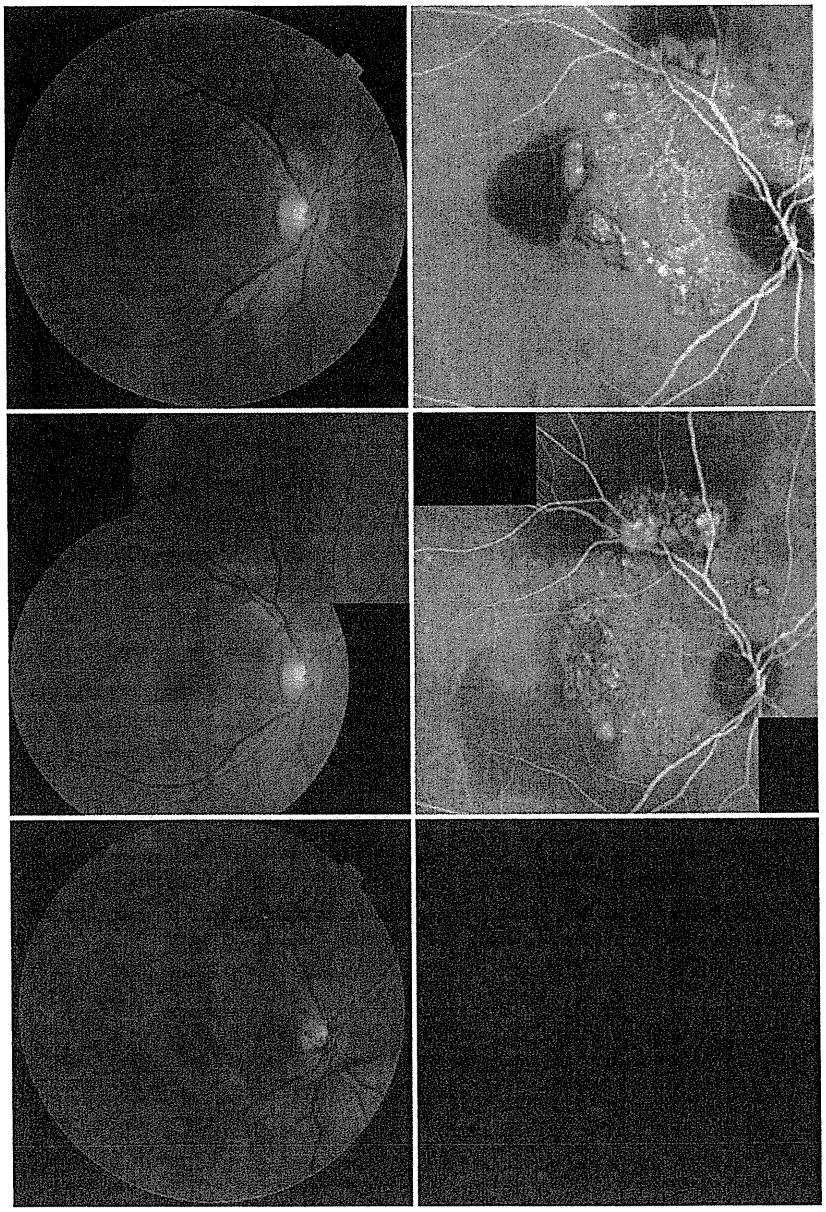

FIGURE 5. Images showing suprachoroidal hemorrhage and vitreous hemorrhage in an eye with larger polypoidal choroidal vasculopathy (PCV). (Top left) Fundus photograph obtained at the initial visit showing multiple large reddish orange nodules; vision was 20/22. (Top right) Indocyanine green angiogram showing a large branching vascular network that terminates with multiple polypoidal lesions. The baseline area of the PCV lesion was 15.80 mm^2. No treatment was performed because this eye had good visual acuity. (Middle left) Fundus photograph obtained at 29 months after the initial visit showing some extension of the vascular components; vision was 20/16. (Middle right) Indocyanine green angiogram showing some extension of the vascular lesion of PCV. (Bottom) Five months after the last angiogram, a sudden suprachoroidal hemorrhage with subsequent vitreous hemorrhage developed in the eye. After vitreous surgery, visual acuity in this eye was only 20/200.

P = .5492) and maintained initial VA to the final visit; mean changes in VA were significantly better in smaller PCV than were those in larger PCV (P = .0015).

Table 2 shows the ocular manifestations and complications seen during follow-up in eyes with smaller or larger PCV. Of the 88 eyes included, 7 (7.6%) showed suprachoroidal hemorrhage and 8 (8.7%) showed vitreous hemorrhage (Figure 5), all of which were seen in eyes with larger PCV; no eyes with smaller PCV showed severe complications (P = .1111 and P = .0868). Indeed, in eyes with smaller PCV, even the relatively small amount of subretinal hemorrhage noted (> 1 DA) was seen less frequently than in eyes with larger PCV (P = .0157). In addition, other ocular manifestations associated with severe visual

TABLE 3. ARMS2 Genotypes and Alleles in Patients with Polypoidal Choroidal Vasculopathy

	Smaller Polypoidal Choroidal Vasculopathy (n = 21)	Larger Polypoidal Choroidal Vasculopathy (n = 55)	*P* Value[a]	Odds Ratio (95% CI)
Genotype			.0397	
TT	3 (10.7%)	25 (89.3%)		5.0 vs GG (3.93 to 6.44)
GT	11 (39.3%)	17 (60.7%)		1.5 vs GG (1.19 to 1.82)
GG	7 (35.0%)	13 (65.0%)		
Allele			.0235	
T	17 (20.2%)	67 (79.8%)		2.4 vs G (2.09 to 2.67)
G	25 (36.8%)	43 (63.2%)		

CI = confidence interval; G = guanine; T = thymine.

One disc area (DA) is estimated as being 2.54 mm^2; this is based on 1 optic disc diameter being 1.8 mm. Based on the area of the lesion at the initial visit, polypoidal choroidal vasculopathy (PCV) eyes were divided into smaller PCV (area of lesion, < 1 DA) and larger PCV (area of lesion ≥ 1 DA).

[a]Chi-square test.

disturbance were seen more often in eyes with larger PCV. Type 2 CNV, subretinal fibrosis, and cystoid macular edema were seen more frequently in eyes with larger PCV ($P = .0030$, $P = .0533$, and $P = .0266$). Of the 88 eyes included in this study, 41 (46.6%) showed a serosanguineous pigment epithelial detachment (area, > 1 DA). Again, a pigment epithelial detachment was seen more frequently in eyes with larger PCV than in those with smaller PCV ($P = .0096$). Of the 88 eyes of our patients, 8 (8.7%) showed a tear of the retinal pigment epithelium. All of these occurred in eyes with larger PCV; no eyes with smaller PCV showed a tear ($P = .0868$).

We were able to examine the deoxyribonucleic acid of 76 of the 88 patients. Table 3 shows the distributions of *ARMS2* (A69S) genotypes in patients with smaller PCV and in those with larger PCV. There was a significant difference in T allele frequency between patients with smaller PCV and those with larger PCV (20.2% vs 79.8%; $P = .0235$). In comparison with wild-type homozygosity (GG), homozygosity for the at-risk genotype (TT) increased the likelihood for the larger PCV group by 5.0-fold, and heterozygosity for the at-risk genotype (GT) increased the likelihood for this same group by 1.5-fold.

DISCUSSION

BASED ON THE INITIAL AREA OF THE VASCULAR LESION, WE defined smaller PCV as those with a baseline area of < 1 DA. The remaining PCV, in which the baseline area was ≥ 1 DA, were defined as larger PCV. There were no significant differences in age or duration of symptoms between these 2 groups. The larger PCV, however, did often show progression of the vascular lesions, which in many instances showed an exudative change. In larger PCV, poor initial VA was even further lessened despite the treatment. In contrast, most eyes diagnosed as having smaller PCV showed only minimal progression of the lesion and limited exudative change. Furthermore, smaller PCV lesions rarely progressed to extensive PCV lesions. Most eyes with smaller PCV had good initial VA and maintained their good VA throughout the follow-up period.

In addition, severe complications such as suprachoroidal hemorrhage, vitreous hemorrhage, and a tear of the retinal pigment epithelium were seen only in eyes with larger PCV; no eyes with smaller PCV showed these severe complications. Furthermore, type 2 CNV and subfoveal fibrosis was seen more frequently in larger PCV. From these findings, we believe that the ocular manifestations, complications, and visual prognosis of smaller PCV are distinct from those of larger PCV. Okubo and associates reported similar findings. Of 13 eyes with PCV that were followed-up for 5 years or longer with no treatment, they reported that eyes with reddish-orange nodules alone or those with nodules plus a small subretinal hemorrhage had a benign clinical course with stable vision.[18]

PCV is thought to have a better visual prognosis than does exudative AMD,[9,20] although the visual prognosis in PCV is not as promising as was thought initially.[21] Previously, direct laser photocoagulation was applied to eyes with PCV.[7,22] Unless the entire vascular lesions could be coagulated, however, the polypoidal lesion often recurred, resulting in decreased VA,[23] although another study showed encouraging short-term results of PDT for PCV.[24] However, 1 year or more after initially successful treatment with PDT, some eyes had a recurrence of PCV and a decrease in VA.[21] Still more recently, although anti-VEGF therapy can reduce the exudative change in PCV shortly after treatment, its effects on the vascular lesions and its

effect on VA seem to be limited.[25–29] In addition, some eyes with large vascular lesions show massive hemorrhagic complications, with sudden visual loss.[30] As shown in Table 2, other vision-threatening complications, such as disciform scar, a tear of the retinal pigment epithelium, or cystoid macular edema, are not as uncommon as reported initially.[16,31,32] Smaller PCV, which often shows a favorable response to treatments and with minimal vision-threatening complications, turn out to have a better visual prognosis than do larger PCV.[17,18]

So far, several classifications of PCV have been reported.[11,12] Based on the location of the lesion, PCV can be categorized as peripapillary, macular, or peripheral.[12] When the vascular lesion is located far from the fovea, visual prognosis tends to be good.[5] Uyama and associates reported 2 patterns of fundus manifestation of PCV, exudative and hemorrhagic.[11] However, they also reported that 36% of the cases had altered their pattern of manifestation during follow-up.[11] Judging from these patterns, it may be difficult to predict visual prognosis.

The polypoidal lesions are thought to be the main source of the exudative change and hemorrhagic complications in PCV.[4,14] Uyama and associates reported 2 patterns of polypoidal lesions: solitary round aneurysmal dilations and a collection of small aneurysmal dilations that resemble a cluster of grapes, the latter of which is associated with a poor prognosis.[11] Clinically, some polypoidal lesions do regress spontaneously, and regress even more after PDT, but these polypoidal lesions recur at the same location or at other terminals of the branching vascular network.[9,12,33] Recently, Cackett and associates reported a classification system of PCV based on polypoidal lesion seen by indocyanine green angiography.[34] In their report,[34] PCV was classified according to size, location, formation, and number of polypoidal lesions. Although objective evaluations are essential for any multicenter study, the branching vascular network, which is one origin of the polypoidal lesions, is essential also to understand status of the disease in each patient.[35]

Based on the results of indocyanine green angiography, Yuzawa and associates reported that there may be 2 types of branching vascular network, one representing an intrachoroidal vascular abnormality, and the other representing neovascularization that grows rapidly in the subretinal pigment epithelial space.[36] Unfortunately, histologic reports of PCV are limited,[37,38] although recent OCT findings support the theory that the vascular components of PCV are located within or above the Bruch membrane. In Figure 4, both the polypoidal lesion and the branching vascular network are seen between the retinal pigment epithelium and Bruch membrane,[39] suggesting that the vascular lesions in PCV are a form of CNV.[14]

The branching vascular network, which only rarely disappeared with treatment, tended to extend over time.[35] It is thought that progression of PCV is slower than that of exudative AMD.[9] Yannuzzi and associates reported that the branching vascular network enlarges by simple proliferation and hypertrophy of the vascular components, by conversion of the polypoidal lesion into the advancing edge of a vascular channel, or by the unfolding of a cluster of polypoidal lesions and subsequent transformation into enlarging vascular tubular components.[9] In the current study, based on the initial size of the vascular components, we divided PCV into smaller and larger types, a classification that provides useful information to both physicians and patients regarding the risk of severe complications and visual prognosis. Smaller PCV rarely progress to become extensive lesions and often have a more favorable clinical course that is quite different from that of larger PCV.[17,18] In the current study, all 15 eyes in which extensive vascular lesions (more than 8 DA) finally developed had a lesion of more than 3 DA at the initial examination. It follows that all eyes with extensive PCV already had shown relatively large vascular lesion when they had initial visual symptoms. From the current study, we could not provide any information on the beginning of the extensive PCV.

In the current study, we examined the genotypes of rs10490924 (A69S) of *ARMS2* in patients with smaller PCV (21 patients) and those with larger PCV (55 patients). An increasing number of reports showed that *ARMS2* A69S is associated strongly with AMD, as well as with typical AMD and with PCV.[40–45] In the current study, there was a significant difference in T allele frequency between the smaller PCV and the larger PCV (20.2% vs 79.8%). Our findings suggest that smaller PCV is different from larger PCV, not only from the clinical point of view but also from the genetic point of view.

In PCV patients, Sakurada and associates reported a difference in the genotypic frequency at this site between eyes with and without vitreous hemorrhage, with the frequency of the T allele being significantly greater in the vitreous hemorrhage group than that in the nonvitreous hemorrhage group.[40] In another report, Sakurada and associates reported that this genotype is not associated with lesion composition or size as seen by indocyanine green angiography.[46] However, they did indicate that the T allele at this SNP is associated with the exudative activity of polypoidal lesions.[46] Although further studies are necessary to elucidate the contribution of this SNP to the progression of the vascular lesion, this SNP seems to be associated with the occurrence of PCV itself and with the activity of the vascular lesions.

Limitations of the current study are its retrospective nature and the various treatment regimens used. Our patents received primarily PDT or anti-VEGF therapy.[25–29] Because recent studies have suggested that PDT in combination with anti-VEGF therapy may be the most promising treatment of PCV, it is possible that our patients did not receive the most effective treatment.[47,48] In the current study, 8 eyes showed a relatively large subretinal hemorrhage at the initial visit. It may be possible that the lesion size was somewhat underestimated in a few eyes.

However, because all of these 8 eyes were classified as having larger PCV, there is no possibility that any eye with a relatively large subretinal hemorrhage was classified incorrectly as having a smaller PCV. In addition, 11 of 22 eyes with smaller PCV still had small lesions (< 1 DA) at the final examination. In remaining 11 eyes, however, the final area of the lesion was more than 1 DA, although the lesion remained relatively small and visual prognosis often was good. If these eyes had been examined later, they might have been classified as having larger PCV. However, despite these shortcomings, our findings suggest that most smaller PCV show limited progression and that good visual function is maintained—with no serious complications. Furthermore, it may be of use to differentiate this type of PCV from larger PCV to prognosticate visual prognosis in affected individuals.

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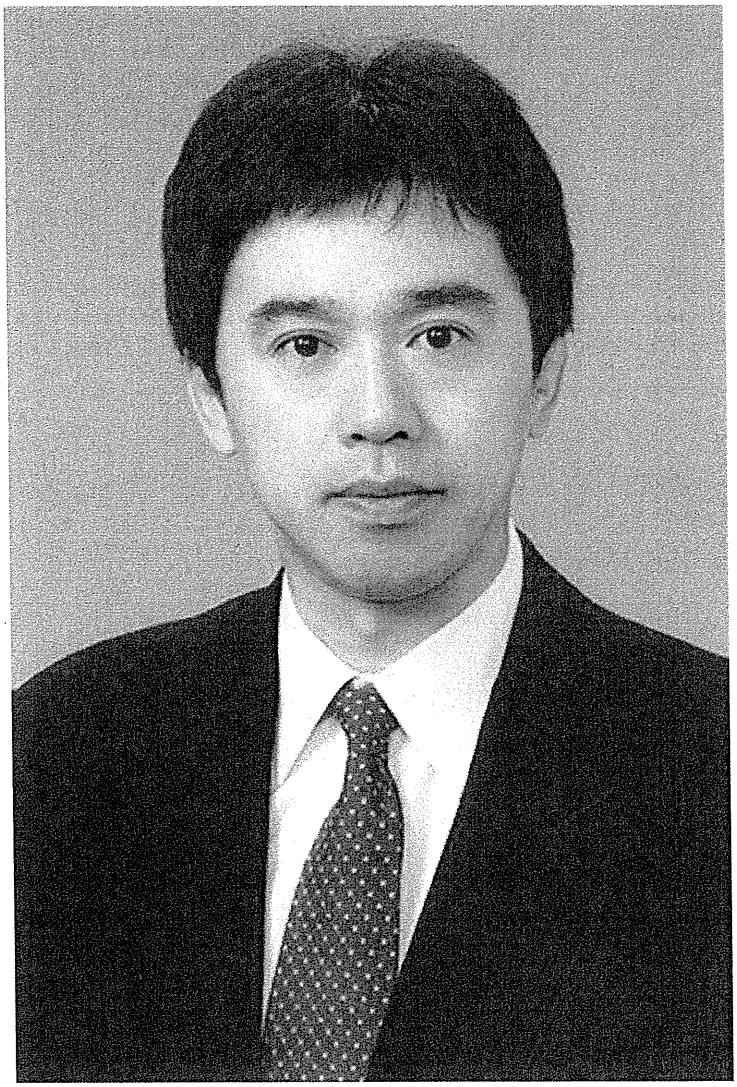

Biosketch

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Genetic Variants in Pigment Epithelium-Derived Factor Influence Response of Polypoidal Choroidal Vasculopathy to Photodynamic Therapy

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Purpose: To investigate whether photodynamic therapy (PDT) outcomes of polypoidal choroidal vasculopathy (PCV) are related to baseline clinical characteristics, smoking history, or genetic factors by analyzing the retreatment-free period after the first PDT.

Design: Retrospective cohort study.

Participants: The study consisted of 167 patients with PCV who underwent PDT as their first treatment.

Methods: We targeted 638 single nucleotide polymorphisms (SNPs) in 42 possible susceptible genes for age-related macular degeneration to evaluate their relation to the effectiveness of PDT for PCV. For this evaluation, we used 2 methods: (1) survival analysis, with the retreatment-free period as the target; and (2) logistic regression test between the need for additional therapy within 3 months after the first PDT and the genotypes, with age, gender, smoking status, and greatest linear dimension (GLD) at baseline as covariates. The contributions of smoking status and GLD at baseline for the retreatment-free period also were evaluated. Contributions of these factors to visual prognosis were evaluated for 1 year after PDT.

Main Outcome Measures: Retreatment-free period after the first PDT for PCV. Secondary outcome measures included correlation of the susceptible factor to the retreatment requirement within the 3-month follow-up and the mean visual acuity change.

Results: In survival analyses, SERPINF1 rs12603825 showed a significant association with the retreatment-free period after the first PDT; those patients homozygous for the minor allele A of rs12603825 received additional treatment after PDT within significantly shorter times than those with other genotypes ($P = 0.0038$). There was no significant difference in the retreatment-free period between baseline GLD and smoking status. Retreatment within 3 months was required significantly more in patients with the AA genotype, even after taking into consideration the effect of clinical characteristics (age, gender), baseline PCV lesion size, and smoking status ($P = 0.0027$). Furthermore, patients with the AA genotype showed significantly worse visual prognosis after PDT ($P = 0.013$).

Conclusions: Pigment epithelium-derived factor (SERPINF1 or PEDF) polymorphisms may influence the initial response to and visual prognosis after PDT for PCV. Our findings may lead to understanding the pathogenesis of PCV and modification of the effects of PDT.

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Polypoidal choroidal vasculopathy (PCV) is observed frequently in Asian patients diagnosed with exudative age-related macular degeneration (AMD),[1,2] and PCV recently has been considered to be a separate clinical entity differing from neovascular AMD and other diseases associated with subretinal neovascularization.[3] Recent studies on the genetics of AMD and PCV have recognized them as complex diseases caused by the actions and interactions of numerous genes and environmental factors.[4–8]

Photodynamic therapy (PDT) with verteporfin was previously one of the main therapeutic options for neovascular AMD, and several studies have shown that the treatment effects of PDT for AMD vary according to the baseline composition, including lesion size of choroidal neovascularization, visual acuity, and genotype.[9–12] Many studies have reported that PDT is more effective in treating PCV than neovascular AMD,[13–15] although PDT for PCV often has to be repeated, either because of persistent disease or

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