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CLINICAL INVESTIGATION

Association of an age-related maculopathy susceptibility 2 gene variant with the 12-month outcomes of intravitreal aflibercept combined with photodynamic therapy for polypoidal choroidal vasculopathy

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Abstract

Purpose To determine the association of age-related maculopathy susceptibility 2 *(ARMS2)* gene polymorphisms with the 12-month outcomes of intravitreal aflibercept combined with photodynamic therapy (IVA+PDT) in polypoidal choroidal vasculopathy (PCV).

Study design Interventional cohort study.

Methods This was a retrospective study of 48 consecutive treatment-naïve PCV patients. The patients underwent IVA+PDT as the initial therapy and were followed up for more than 12 months under a pro re nata regimen. The single nucleotide polymorphism (SNP) at rs10490924 in the *ARMS2* gene was genotyped using the TaqMan assay. The clinical characteristics and outcomes of IVA+PDT were compared among the 3 genotypes at rs10490924. Multivariate regression analysis was performed to evaluate the influence of the clinical cofactors on the association of rs10490924 with the visual outcome at 12 months after the first IVA+PDT.

Results No significant difference was found in the baseline characteristics among the 3 genotypes (n = 9, 23, and 16 for the GG, GT, and TT genotypes, respectively). All the patients, regardless of genotype, showed a significant improvement in vision, central retinal thickness, and subfoveal choroidal thickness at all time points measured after the initial IVA+PDT. The number of treatments was significantly smaller in the patients with the GG genotype than in those with the GT or the TT genotype. On multivariate logistic regression analysis, the number of the T allele at rs10490924 was significantly associated with the chance of retreatment after the initial IVA+PDT.

Conclusion The presence of the G allele at rs10490924 in the *ARMS2* gene is likely associated with a lower chance of retreatment after IVA+PDT in patients with PCV.

Keywords Combination · Aflibercept · Photodynamic therapy · Polymorphism · 12 month outcome

Introduction

Polypoidal choroidal vasculopathy (PCV) is recognized as a phenotype of age-related macular degeneration (AMD), a major cause of blindness in older adults globally [1]. PCV has some characteristics such as orange-red protrusions at the posterior pole of the retina and distinct forms of choroidal vascular abnormalities, including characteristic polypoidal lesions with or without vascular networks of choroidal origin found on indocyanine green angiography (ICGA) [2]. Since PCV is a major phenotype of Japanese wet AMD [3, 4], development of an optimal protocol to treat PCV is an important issue in Japan.

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Intravitreal injection of aflibercept (IVA), an antivascular endothelial growth factor (VEGF) agent, is a treatment of choice for PCV, and several studies have reported significant improvements in the vision of PCV patients with IVA [5–7]. However, IVA monotherapy requires frequent injections to maintain the patient's vision, which may burden the patient in terms of expenses and side-effects represented by the secondary geographic atrophy [8, 9]. Photodynamic therapy (PDT) with verteporfin is an older modality than anti-VEGF but is known to be effective in certain types of PCV [10–12], and a recent randomized controlled trial has revealed that PDT is an effective modality to be combined with anti-VEGF therapies for PCV [13]. However, whether this combination therapy is effective for all PCV cases is unknown, and no definitive criterion to determine PDT responders exists. Several genetic association studies were conducted to predict the outcomes of PDT monotherapy in PCV patients [14–18] since genetic information is case-specific and could be used by every physician without any diagnostic biases; hence, finding reliable genetic variants associated with the outcomes of therapy would be a constructive strategy. In addition, recent commercial genotyping services enable patients and physicians to obtain individual genotypes within a shorter time period and at a lower cost. Using genetic information to choose interventions is anticipated to be more common in future clinical practice [19]. Previously, we reported that genetic variants of rs10490924 (A69S) in the age-related maculopathy susceptibility 2 *(ARMS2)* gene were associated with the 12-month and 36-month visual outcomes of PDT in patients with wAMD [17, 18], and similar results were reported by other groups over 12 months of follow-up [14, 16]. However, only 1 study has been published to date regarding the genetic association with the outcomes of IVA+PDT over 12-months of follow-up [20].

In this study, we investigated the association of rs10490924 in *ARMS2* with the 12-month outcomes of IVA+PDT in patients with PCV.

Patients and methods

Study participants

This study was approved by the institutional review board of the Kobe University Graduate School of Medicine (No. 467) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients. All of them were Japanese individuals who consented to DNA sampling and were recruited from the Department of Ophthalmology of Kobe University Hospital.

Forty-eight eyes of 48 consecutive patients with PCV who underwent IVA+PDT as the initial treatment and were then followed up for more than 12 months were retrospectively included in this study.

Examinations and treatments

All the patients received detailed ophthalmic examinations, including best-corrected visual acuity (BCVA) measurements, slit-lamp biomicroscopy of their fundi, color fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICGA) (HRA2; Heidelberg Engineering), and spectral-domain optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering) before starting treatment. The diagnosis of PCV was made in accordance with a previous report [21]. In fact, the PCV patients in this study showed subretinal reddish orange protrusions corresponding to the choroidal origin of the polypoidal lesions, typically with the vascular networks in the posterior poles on ICGA. Patients were excluded if they had received any previous treatment such as laser photocoagulation, vitrectomy, or intravitreal anti-VEGF therapy or if they had histories of retinal vessel occlusion, diabetic retinopathy, uveitis, rhegmatogenous retinal detachment, or glaucoma.

In this study, all the patients received IVA (2.0 mg/0.05-mL aflibercept injection) and standard vPDT (a laser light at 689 nm delivered at a dose of 50 J/cm^2 at an intensity of 600 mW/cm^2 over 83 seconds) with verteporfin (6 mg/m^2) a week later as induction therapy. The laser spot size was determined as 1000 μm added to the area of any polyps and branching vascular network on the ICGA findings [22]. After the initial treatment, the patients were followed up with a pro re nata regimen until 12 months after the initial treatment, as previously described [23]. Essentially, they were followed up monthly with examinations including BCVA measurements, slit-lamp biomicroscopy, and OCT images until 12 months from the initial treatment. The criteria for ordering additional treatments were as follows: (1) if exudative changes such as subretinal or intraretinal fluid were found on OCT; (2) a combination of IVA and PDT was performed if residual polyp lesions were found on ICGA; and (3) IVA monotherapy was performed if no residual polyp lesion was found on ICGA. Routine FA and ICGA were scheduled at 3 months and 12 months of follow-up, and additional FA/ICGA were allowed at the physician's discretion.

Genotyping

Genomic DNA was extracted from the peripheral blood using a standard method. Genotyping was performed using TaqMan SNP Genotyping Assays or Custom TaqMan SNP Genotyping Assays (Applied Biosystems) on a StepOnePlus Real-Time PCR System (Applied Biosystems) in accordance with the supplier's recommendations.

Indices compared

The age, sex, lesion size (GLD: greatest linear dimension) based on the ICGA findings and the baseline best-corrected visual acuity (BCVA) were compared among the 3 genotypes of rs10490924 in *ARMS2*. These parameters were measured for each case under masked conditions for genotype. The primary outcome measures were the change in the BCVA at 12 months after the initial PDT. The rate of complete polyp regression and anatomic changes from baseline including central retinal thickness (CRT) and subfoveal choroidal thickness (SFCT) as assessed by OCT were measured as the secondary outcomes. The number of treatments over the 12 months of follow-up was also evaluated. To identify the factors useful for predicting the change in the outcomes at 12 months post-PDT, multivariate regression analyses were performed. The explanatory variables included sex, age, baseline BCVA, GLD, presence or absence of PCV, and number of the T (risk) allele at rs10490924 in *ARMS2*. Dummy variables were applied for sex (female = 1, male = 0).

Statistical analysis

All statistical analyses were performed using R version 3.1.1 software. The parameters were compared among the 3 genotypes using the Fisher exact test, the Kruskal–Wallis test, or univariate regression analysis, where applicable. For the time course analysis, 2 time points in each genotype were compared using a paired *t* test (2-tail). Probability values less than .05 were considered significant.

Results

The clinical characteristics of the PCV patients stratified by the genotypes of rs10490924 in *ARMS2* are presented in Table 1. In the baseline parameters, other than gender ($P = 0.044$), no significant differences were found among the 3 genotypes (n = 9, 23, and 16 for the GG, GT, and TT genotypes, respectively).

At 12 months post-PDT, the patients with the GG, GT, and TT genotypes showed a significant improvement in BCVA (−0.18 ± 0.11, −0.11 ± 0.12, −0.13 ± 0.19 logMAR and $P = 0.0011$, 0.00016, 0.016, respectively; Fig. 1a); in CRT (−118.9 ± 141.4, −165.0 ± 149.2, −245.3 ± 294.8 µm and $P = 0.036$, 0.000039, 0.0046, respectively; Fig. 1b); and in SFCT (−43.2 ± 25.7, −44.2 ± 82.2, −35.2 ± 45.7 µm and $P = 0.00053$, 0.0027, 0.0076, respectively; Fig. 1c). No significant differences in those parameters were found among the 3 genotypes. In contrast, the number of the T allele was significantly associated with a larger number of injections over 12 months of follow-up ($P = 0.034$; Table 2). The results of the stepwise multivariate regression analysis conserved the significance of the association of the rs10490924 (A69S) variants with the number of injections (Table 3).

The proportions of the patients who required any retreatment (IVA monotherapy or IVA+PDT) were 11.1%, 56.5%, and 68.8% in the GG, GT, and TT groups, respectively (Fig. 2a). Namely, 61.5% of the patients with the GT or TT genotype required retreatments, whilst no additional treatment was required in 88.9% of the patients with the GG genotype over 12 months of follow-up, which was significantly different ($P = 0.0090$, Fisher exact test; Fig. 2b).

No ocular or systemic complications were reported during the follow-up period.

Table 1 Clinical characteristics stratified by the A69S genotype in the *ARMS2* gene

Parameter	GG (n = 9)	GT (n = 23)	TT (n = 16)	*P* value
Sex (M/F)	5/4	15/8	15/1	0.044†
Age (years)	71.9 ± 9.4	74.7 ± 8.7	72.9 ± 12.2	0.858*
GLD (µm)	2878.9 ± 1016.2	2385.2 ± 1220.2	3741.3 ± 2385.9	0.104*
Baseline BCVA (logMAR)	0.27 ± 0.24	0.13 ± 0.17	0.32 ± 0.45	0.235*
Baseline CRT (µm)	286.1 ± 127.8	384.0 ± 157.7	416.7 ± 291.6	0.381*
Baseline SFCT (µm)	229.4 ± 75.8	246.8 ± 97.5	187.1 ± 73.2	0.133*
Number of polyps	1.7 ± 1.1	1.5 ± 0.8	2.1 ± 1.5	0.559*

Values are presented as means ± SDs where applicable

GLD greatest linear dimension, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimum angle of resolution, *CRT* central retinal thickness, *SFCT* subfoveal choroidal thickness

†Fisher exact test

*Kruskal–Wallis test

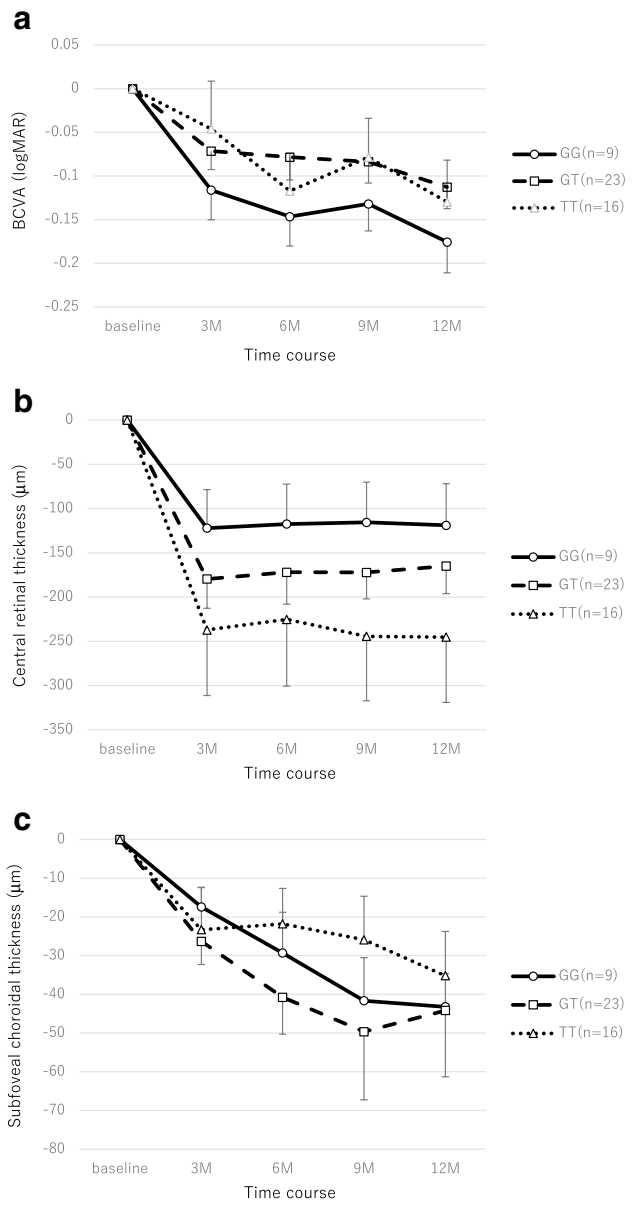

Fig. 1 Time course after the initial IVA+PDT for PCV patients stratified by the genotypes of A69S in the *ARMS2* gene. Influence of the genotype at rs10490924 (A69S) in *ARMS2* on the chronologic changes in **a** BCVA (logMAR), **b** central retinal thickness, and **c** subfoveal choroidal thickness in PCV patients treated with IVA+PDT. All values are presented as means ± SEMs. *IVA* intravitreal injection of aflibercept, *PDT* photodynamic therapy, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimum angle of resolution. Circles with solid line: GG genotype (n = 9); squares with dashed line: GT genotype (n = 23); triangles with dotted line: TT genotype (n = 16)

Discussion

We evaluated the association of a well-recognized SNP in *ARMS2* with the 12-month outcomes of IVA+PDT in PCV patients and found that the genotype at rs10490924 (A69S) in *ARMS2* was significantly associated with the number of injections at 12 months after their initial IVA+PDT. Namely, patients with the GG genotype at rs10490924 required significantly fewer injections than did patients with the other genotypes until 12 months after the initial PDT.

Table 2 Number of treatments among the A69S genotypes in the *ARMS2* gene

Treatment	GG (n = 9)	GT (n = 23)	TT (n = 16)	*P* value
IVA (mean ± SD)	1.3 ± 1.0	2.0 ± 1.3	2.9 ± 2.4	0.034*
PDT (mean ± SD)	1.1 ± 0.3	1.2 ± 0.4	1.4 ± 0.6	0.476*

IVA intravitreal injection of aflibercept, *PDT* photodynamic therapy
*Kruskal–Wallis test

Previous genetic association studies have performed comparative assessments for the association of rs10490924 (A69S) in *ARMS2* among 3 different phenotypes of wAMD [24–27], the results of which suggested heterogeneities in the association of this SNP within the AMD phenotype spectrum. The association of *ARMS2* variants with the outcomes of established therapies for wAMD has also been reported in several cohorts [14–18, 20, 28] In particular, a recent study indicated a significant association of *ARMS2* variants with the 24-month outcomes of intravitreal ranibizumab+PDT and IVA+PDT in PCV patients [20], but the authors of that study also pointed out the need for replication studies with other cohorts. The present study has demonstrated the beneficial effect of the G allele (nonrisk allele) at rs10490924 (A69S) in *ARMS2* on the chance of recurrence after the initial IVA+PDT in PCV patients, which is consistent with the findings of a previous report [20]. We could not detect a significant association of this variant with the visual outcome of IVA+PDT, but this might be due to insufficient statistical power to detect a significant association, because the patients with the GG genotype showed relatively better visual prognosis than did the other genotypes. As for CRT, the GG genotype showed the smallest reduction among the 3 genotypes, probably because the baseline CRT was the smallest, though not significant, which may have caused a ceiling effect.

The role of *ARMS2* in PDT is unknown. Recent reports have demonstrated that *ARMS2* can affect the lesion size [17, 29] and progression of wAMD [30, 31], which may influence the visual outcome post-PDT. Kanda and colleagues reported that ARMS2 distributes to the outer membrane of the mitochondria and may be involved in the regulation of oxidative stresses [32]. Reactive oxygen species play a key role by which PDT affects neovascular endothelial cells, followed by thrombosis and occlusion of the neovascular tracts [33]. The *ARMS2* genotype is also possibly associated with the PCV subtype (ie, type 1 PCV and type 2 PCV) [34, 35], resulting in a differential response rather than a direct

Table 3 Prognostic factors for the number of treatments at 12 months after IVA+PDT: stepwise multiple regression analysis results

Prognostic factors	SPRC	SEM	*t* value	*P* value
Number of T (risk) allele at rs10490924 in *ARMS2*	0.82	0.29	2.85	.0176

Multiple R-squared: 0.28

SPRC standardized partial regression coefficient, *SEM* standard error of the mean

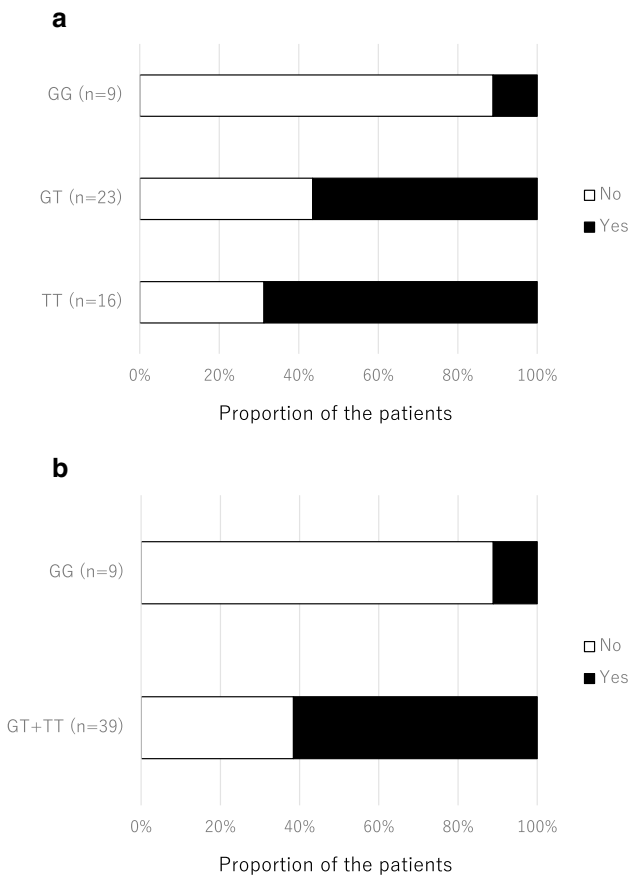

Fig. 2 Need for retreatment after the initial therapy associated with A69S genotypes in the *ARMS2* gene. The proportions of patients who required any retreatment are compared according to **a** 3 A69S genotypes (GG, GT, and TT) in the *ARMS2* gene or **b** between the GG and GT+TT groups

effect on PDT itself [36]. However, the result of stepwise multiple regression analysis indicated the *ARMS2* genotype as an independent contributor to the chance of recurrence after the initial IVA+PDT. A recent report has demonstrated that the *ARMS2* genotype was associated with the chance of recurrence after 3-monthly IVA monotherapy with a pro re nata regimen [37]. Over 40% of the patients with the GG genotype and 80% of the patients with the TT genotype in that study had a recurrence over 12 months of follow-up. We considered that the GG genotype may be beneficial both in IVA monotherapy and in IVA+PDT, but the ability to suppress recurrence might be stronger in IVA+PDT for PCV patients. Further studies will be needed to disclose the certain role of *ARMS2* in the pathogenesis of PCV and the mechanism whereby IVA+PDT works to treat PCV. Nevertheless, the present study demonstrated that PCV patients with the GG genotype would be good candidates for IVA+PDT, which suggests that the assessment of genetic information is likely useful for evaluating the applicability of PDT to be combined with IVA in PCV patients.

The limitations of the present study were its relatively small sample size and retrospective nature. For example, the group with the TT genotype had significantly fewer female patients, relatively larger lesions, and worse baseline BCVA than did the groups with the other genotypes. Although multivariate analysis did not select those as significant factors, a replication study with a larger cohort may be needed to confirm the results. In addition, a prospective study for the outcome of IVA+PDT would be useful to disclose further association of *ARMS2* variants with the effect of IVA+PDT in PCV patients.

Although PDT is known to induce a number of gene expression changes in the retina-choroid complex [33, 38], the detailed mechanisms by which multiple genes interact with each other to close polypoidal lesions is poorly understood. However, our results suggest that genetic association studies provide some clinical possibilities that can be applied for personalized therapies in individual PCV patients.

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References

1. Cook HL, Patel PJ, Tufail A. Age-related macular degeneration: diagnosis and management. Br Med Bull. 2008;85:127–49.
2. Rein DB, Wittenborn JS, Zhang X, Honeycutt AA, Lesesne SB, Saaddine J, Vision Health Cost-Effectiveness Study Group. Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. Arch Ophthalmol. 2009;127:533–40.

3. 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;144:15–22.
4. Tsujikawa A, Akagi-Kurashige Y, Yuzawa M, Ishibashi T, Nakanishi H, Nakatani E, AMD2000 Study Group, et al. Baseline data from a multicenter, 5-year, prospective cohort study of Japanese age-related macular degeneration: an AMD2000 report. Jpn J Ophthalmol. 2018;62:127–36.
5. Yamamoto A, Okada AA, Kano M, Koizumi H, Saito M, Maruko I, et al. One-year results of intravitreal aflibercept for polypoidal choroidal vasculopathy. Ophthalmology. 2015;122:1866–72.
6. Hara C, Sawa M, Sayanagi K, Nishida K. One-year results of intravitreal aflibercept for polypoidal choroidal vasculopathy. Retina. 2016;36:37–45.
7. Saito M, Kano M, Itagaki K, Sekiryu T. Efficacy of intravitreal aflibercept in Japanese patients with exudative age-related macular degeneration. Jpn J Ophthalmol. 2017;61:74–83.
8. Alexandru MR, Alexandra NM. Wet age related macular degeneration management and follow-up. Rom J Ophthalmol. 2016;60:9–13.
9. Enslow R, Bhuvanagiri S, Vegunta S, Cutler B, Neff M, Stagg B. Association of anti-VEGF injections with progression of geographic atrophy. Ophthalmol Eye Dis. 2016;8:31–2.
10. Nowak-Sliwinska P, van den Bergh H, Sickenberg M, Koh AH. Photodynamic therapy for polypoidal choroidal vasculopathy. Prog Retin Eye Res. 2013;37:182–99.
11. Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Fujisan Study Group, et al. Initial versus delayed photodynamic therapy in combination with ranibizumab for treatment of polypoidal choroidal vasculopathy: the Fujisan Study. Retina. 2015;35:1569–76.
12. Honda S, Imai H, Yamashiro K, Kurimoto Y, Kanamori-Matsui N, Kagotani Y, et al. Comparative assessment of photodynamic therapy for typical age-related macular degeneration and polypoidal choroidal vasculopathy: a multicenter study in Hyogo prefecture, Japan. Ophthalmologica. 2009;223:333–8.
13. Koh A, Lai TYY, Takahashi K, Wong TY, Chen LJ, Ruamviboonsuk P, EVEREST II study group, et al. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. JAMA Ophthalmol. 2017;135:1206–13.
14. Tsuchihashi T, Mori K, Horie-Inoue K, Gehlbach PL, Kabasawa S, Takita H, et al. Complement factor H and high-temperature requirement A-1 genotypes and treatment response of age-related macular degeneration. Ophthalmology. 2011;118:93–100.
15. Brantley MA Jr, Edelstein SL, King JM, Plotzke MR, Apte RS, Kymes SM, et al. Association of complement factor H and LOC387715 genotypes with response of exudative age-related macular degeneration to photodynamic therapy. Eye (Lond). 2009;23:626–31.
16. 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;30:1616–21.
17. Bessho H, Honda S, Kondo N, Negi A. The association of age-related maculopathy susceptibility 2 polymorphisms with phenotype in typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Mol Vis. 2011;17:977–82.
18. Nakai S, Honda S, Matsumiya W, Miki A, Nakamura M. *ARMS2* variants may predict the 3-year outcome of photodynamic therapy for wet age-related macular degeneration. Mol Vis. 2017;23:514–9.
19. Brunicardi FC, Gibbs RA, Wheeler DA, Nemunaitis J, Fisher W, Goss J, et al. Overview of the development of personalized genomic medicine and surgery. World J Surg. 2011;35:1693–9.
20. Kikushima W, Sakurada Y, Sugiyama A, Yoneyama S, Tanabe N, Matsubara M, et al. Comparison of two-year outcomes after photodynamic therapy with ranibizumab or aflibercept for polypoidal choroidal vasculopathy. Sci Rep. 2017;7:16461.
21. Japanese Study Group of Polypoidal Choroidal Vasculopathy. Criteria for diagnosis of polypoidal choroidal vasculopathy [in Japanese]. Nippon Ganka Gakkai Zasshi. 2005;109:417–27.
22. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin One-year results of 2 randomized clinical trials: TAP report 1. Arch Ophthalmol. 1999;117:1329–45.
23. Matsumiya W, Honda S, Otsuka K, Miki A, Nagai T, Imai H, et al. One-year outcome of combination therapy with intravitreal aflibercept and verteporfin photodynamic therapy for polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol. 2017;255:541–8.
24. 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;144:608–12.
25. Hayashi H, Yamashiro K, Gotoh N, Nakanishi H, Nakata I, Tsujikawa A, et al. *CFH* and *ARMS2* variations in age-related macular degeneration, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation. Invest Ophthalmol Vis Sci. 2010;51:5914–9.
26. Goto A, Akahori M, Okamoto H, Minami M, Terauchi N, Haruhata Y, et al. Genetic analysis of typical wet-type age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese population. J Ocul Biol Dis Inform. 2009;2:164–75.
27. Gotoh N, Nakanishi H, Hayashi H, Yamada R, Otani A, Tsujikawa A, et al. *ARMS2 (LOC387715)* variants in Japanese patients with exudative age-related macular degeneration and polypoidal choroidal vasculopathy. Am J Ophthalmol. 2009;147(1037–41):e2.
28. Hu Z, Xie P, Ding Y, Yuan D, Liu Q. Association between variants A69S in ARMS2 gene and response to treatment of exudative AMD: a meta-analysis. Br J Ophthalmol. 2015;99:593–8.
29. Tsujikawa A, Ojima Y, Yamashiro K, Nakata I, Ooto S, Tamura H, et al. Association of lesion size and visual prognosis to polypoidal choroidal vasculopathy. Am J Ophthalmol. 2011;151:961–72.
30. Joachim N, Mitchell P, Burlutsky G, Kifley A, Wang JJ. The incidence and progression of age-related macular degeneration over 15 years: the Blue Mountains Eye Study. Ophthalmology. 2015;122:2482–9.
31. Seddon JM, Silver RE, Kwong M, Rosner B. Risk prediction for progression of macular degeneration: 10 common and rare genetic variants, demographic, environmental, and macular covariates. Invest Ophthalmol Vis Sci. 2015;56:2192–202.
32. Kanda A, Chen W, Othman M, Branham KE, Brooks M, Khanna R, et al. A variant of mitochondrial protein LOC387715/ARMS2, not HTRA1, is strongly associated with age-related macular degeneration. Proc Natl Acad Sci USA. 2007;104:16227–32.
33. van den Bergh H. Photodynamic therapy of age-related macular degeneration: history and principles. Semin Ophthalmol. 2001;16:181–200.
34. Tanaka K, Nakayama T, Mori R, Sato N, Kawamura A, Mizutani Y, et al. Associations of complement factor H (*CFH*) and age-related maculopathy susceptibility 2 (*ARMS2*) genotypes with subtypes of polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci. 2011;52:7441–4.
35. Miki A, Honda S, Kondo N, Negi A. The association of age-related maculopathy susceptibility 2 (*ARMS2*) and complement factor H (*CFH*) variants with two angiographic subtypes of polypoidal choroidal vasculopathy. Ophthalmic Genet. 2013;34:146–50.

36. Honda S, Miki A, Yanagisawa S, Matsumiya W, Nagai T, Tsukahara Y. Comparison of the outcomes of photodynamic therapy between two angiographic subtypes of polypoidal choroidal vasculopathy. Ophthalmologica. 2014;232:92–6.
37. Kikushima W, Sakurada Y, Yoneyama S, Sugiyama A, Tanabe N, Kume A, et al. Incidence and risk factors of retreatment after three-monthly aflibercept therapy for exudative age-related macular degeneration. Sci Rep. 2017;7:44020.
38. She H, Nakazawa T, Matsubara A, Connolly E, Hisatomi T, Noda K, et al. Photoreceptor protection after photodynamic therapy using dexamethasone in a rat model of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2008;49:5008–14.