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Genetic factors associated with treatment response to reduced-fluence photodynamic therapy for chronic central serous chorioretinopathy

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Purpose: Reduced-fluence photodynamic therapy (RFPDT) has proven effective for some patients with chronic central serous chorioretinopathy (cCSC). Several clinicodemographic factors influencing treatment response have been identified, but associations with genetic factors have not been examined. Therefore, we investigated the associations of single nucleotide polymorphisms (SNPs) implicated in cCSC pathogenesis with clinical outcome following RFPDT.
Methods: This was a retrospective study of 87 eyes from 87 patients with cCSC who underwent RFPDT and were followed up for more than 12 months. Patients were divided into a good response group (53 patients) and a poor response group (34 patients) based on either persistence or recurrence of subretinal fluid detected with spectral domain optical coherence tomography after the first application of RFPDT. SNPs in the genes encoding age-related maculopathy susceptibility protein 2 (*ARMS2*, SNP rs10490924) and complement factor H (*CFH*, SNP rs800292) were genotyped using TaqMan technology.
Results: There were no statistically significant differences in the baseline characteristics between the response groups except the degree of hyperfluorescence on indocyanine green angiography (ICGA; p = 0.011). The minor (T) allele frequency of *ARMS2* (rs10490924) were statistically significantly lower in the good response group than in the poor response group (24.0% versus 41.0%, p = 0.021). Further, the good response frequency was statistically significantly lower in patients with at least one minor allele (GT or TT) compared to the homozygous major allele group (GG; p<0.05). The baseline best-corrected visual acuity (BCVA) at 12 months after RFPDT was statistically significantly better in the GG carriers than in the GT or TT carriers (p<0.01). Logistic regression analysis showed less intense hyperfluorescence on ICGA, and the T allele of *ARMS2* (rs10490924) was statistically significantly associated with poor response to PDT treatment (p = 0.012, p = 0.039, respectively).
Conclusions: Carriers of the *ARMS2* rs10490924 minor allele (GT or TT) demonstrated a higher subretinal fluid persistence or recurrence rate and poorer visual outcome following RFPDT. In addition to the ICGA findings, genotyping of *ARMS2* (rs10490924) may assist in the selection of patients with cCSC most likely to benefit from RFPDT.

Central serous chorioretinopathy (CSC) causes retinal detachment, typically involving the macula, due to subretinal fluid (SRF) accumulation [1]. Although CSC usually resolves spontaneously within 3 months, treatment should be considered when SRF accumulation persists beyond this period.

Previous studies have demonstrated that reduced-fluence photodynamic therapy (RFPDT) is effective for some patients with chronic CSC (cCSC) [2,3]. However, other patients experience persistent or recurrent SRF accumulation after the first application of RFPDT. Lower baseline best-corrected visual acuity (BCVA), older age, and male sex are associated with SRF recurrence or persistence [4,5]. In contrast to these clinicodemographic factors, no genetic factors predictive of CSC treatment response have been identified.

We previously reported an association between the single nucleotide polymorphism (SNP) *CFH* (Gene ID 3075, OMIM 134370) I62V (rs800292) and cCSC [6]. Similarly, Yong et al. [7] reported associations between cCSC and *CFH* I62V (rs800292) and *ARMS2* (Gene ID 387715, OMIM 611313) A69S (rs10490924). Given the putative involvement of these SNPs in cCSC pathogenesis, we investigated associations with RFPDT response.

METHODS

All investigations adhered to the tenets of the Declaration of Helsinki and the ARVO Statement on Human Subjects. The study protocol was approved by the institutional review board of Kobe University Hospital, and written informed consent was obtained from all patients. Medical records of patients

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with cCSC who underwent RFPDT and were followed up for more than 12 months at Kobe University Hospital were retrospectively reviewed.

The inclusion criteria were as follows: (1) SRF accumulation involving the fovea as revealed by optical coherence tomography (OCT), (2) active angiographic leakage caused by CSC as shown by fluorescein angiography (FA), (3) abnormally dilated choroidal vessels as shown by indocyanine green angiography (ICGA), and (4) follow-up for at least 12 months after RFPDT. The exclusion criteria were as follows: (1) evidence of choroidal neovascularization; (2) any other ocular disease that could affect visual acuity, including tilted disc syndrome, dome shaped macula, and uveitis; (3) history of transpupillary thermotherapy (TTT); and (4) media opacities such as cataracts that could interfere with OCT, FA, and ICGA. Chronic CSC was defined as SRF accumulation persisting for more than 3 months before RFPDT.

Patients were divided into a good response group and a poor response group based on either persistence or recurrence of SRF accumulation as detected with spectral domain OCT after the first application of RFPDT. The good response group demonstrated complete resolution and no recurrence of SRF on OCT after the first treatment. The poor response group exhibited incomplete resolution of SRF within 2 months or recurrence of SRF after the first treatment.

All patients received an infusion of verteporfin (Visudyne; Novartis, Basel, Switzerland) at 6 mg/m^2 body surface area over 10 min. Laser treatment was initiated 15 min after the start of infusion. Standard light intensity was 600 mW/cm^2, and the irradiation time was 42 s (half-time PDT). Genotyping of the SNPs *ARMS2* A69S (rs10490924) and *CFH* I62V (rs800292) was conducted using TaqMan technology (Thermo Fisher Scientific, Waltham, MA).

All patients received a complete ophthalmologic examination at baseline, including a slit-lamp examination, a dilated fundus examination, and measurement of BCVA. A Heidelberg Spectralis OCT system (Heidelberg Engineering GmbH, Heidelberg, Germany) was used for macular scans and choroidal imaging, and a Heidelberg Spectralis HRA2 system was used for digital FA and ICGA. We investigated the presence of retinal pigment epithelium (RPE) alterations reported to be seen in cCSC eyes, including RPE atrophy, descending tract, and irregular RPE detachment. The degree of hyperfluorescence on ICGA was also evaluated with reference to a previous study by Inoue et al. [8]. We measured the central foveal thickness (CFT) from the outer surface of the neurosensory retina to the inner surface of the RPE and the subfoveal choroidal thickness (SCT) from the outer surface of the RPE to the inner surface of the sclera. For the Spectralis OCT examinations, average scores of horizontal and vertical line scans through the fovea were obtained. If a patient received RFPDT for both eyes, we analyzed the right eye.

Data are presented as mean ± standard deviation or proportion (%) as appropriate. The decimal visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) for statistical analyses. Continuous variables were compared with the Mann–Whitney U test and categorical variables with a chi-square test. A p value of less than 0.05 was considered statistically significant for all tests. All statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY).

RESULTS

Eighty-seven eyes of 87 patients were included in this study. The baseline characteristics of both groups are summarized in Table 1. There were no statistically significant differences in mean age, sex ratio, smoking, pretreatment cCSC duration, spot size, the presence of RPE alteration, baseline CFT, and baseline SCT between the good response group (53 eyes) and the poor response group (34 eyes), except the degree of hyperfluorescence on ICGA ($p = 0.011$). The baseline BCVA was slightly higher in the good response group, but the difference did not reach significance ($p = 0.069$,). The minor allele frequencies of the genotyped SNPs are shown in Table 2. There was no statistically significant difference in the *CFH* I62V (rs800292) minor allele frequency between the groups ($p = 0.56$), but the minor allele (T) frequency of *ARMS2* (rs10490924) differed statistically significantly between the response groups ($p = 0.021$). The proportion of patients with a good response to RFPDT was statistically significantly higher among the homozygous major allele carriers (GG) than among the combined minor allele (GT+TT) carriers (70.2% versus 50%; $p<0.05$, Figure 1). Although there were no statistically significant differences in BCVA at baseline between the GG and GT+TT groups, BCVA at 12 months after RFPDT was statistically significantly better in the GG group ($p<0.01$; Table 3).

Next, we investigated the correlation between the T allele of *ARMS2* (rs10490924) and the degree of hyperfluorescence on the ICGA findings with statistically significant differences in the response to PDT treatment and found that there was no statistical significance ($p = 0.378$). We also performed logistic regression analysis to investigate factors related to the response to the PDT treatment and found that less-intense hyperfluorescence on the ICGA findings and the presence of the T allele of *ARMS2* (rs10490924) showed statistically significant associations with the poor response to the PDT treatment (Table 4).

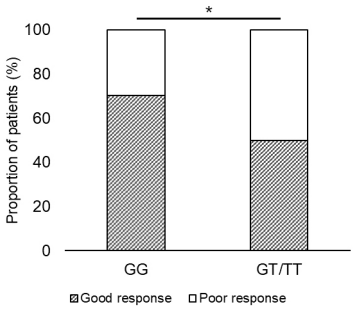

Figure 1. Impact of *ARMS2* polymorphisms on the response of patients with cCSC to RFPDT. The proportion of patients with a good response to reduced-fluence photodynamic therapy (RFPDT) was statistically significantly higher in the homozygous major allele group (GG) compared to carriers of the minor allele (GT+TT). *p<0.05 (chi-square test).

Table 1. Patient demographic and baseline clinical characteristics.

Factor	Good treatment response (n=53)	Poor treatment response (n=34)	P value
Age (years)	55.1±12.3	61.1±16.2	0.11
Sex (male/female)	39/14	23/11	0.50
Baseline BCVA (logMAR)	0.13±0.27	0.21±0.28	0.069
Smoking (+/−)	14/39	9/25	0.59
Disease duration (months)	12.6±20.1	14.8±17.5	0.106
Spot size (µm)	4123.1±1175.5	4233.3±1361.6	0.71
RPE alteration (+/−)	33/20	20/14	0.46
Hyperfluorescence on ICGA findings (Intense/Intermediate/No)	15/29/9	6/12/16	0.011
Baseline CFT (µm)	330.7±103.8	339.9±117.5	0.62
Baseline SCT (µm)	401.9±119.6	342.3±117.3	0.70

Continuous variables presented as mean ± SD BCVA, best-corrected visual acuity; logMAR, logarithmic minimum angle of resolution; RPE, retinal pigment epithelium; ICGA, indocyanine green angiography; CFT, central foveal thickness; SCT, subfoveal choroidal thickness.

Table 2. Genotypes of cCSC patients according to RFPDT response.

Single nucleotide polymorphism	Allele	Good response MAF	Poor response MAF	P value
ARMS2 (rs10490924)	G/T	0.24	0.41	0.021
CFH I62V (rs800292)	G/A	0.47	0.43	0.56

cCSC, chronic central serous chorioretinopathy; MAF, minor allele frequency; RFPDT, reduced-fluence photodynamic therapy.

Table 3. Clinical outcomes of cCSC patients according to ARMS2 genotype.

BCVA (logMAR)	ARMS2 (rs10490924)		P value
	GG	GT + TT	
baseline	0.12 ± 0.28	0.20 ± 0.26	0.15
12 months after RFPDT	−0.022 ± 0.19	0.13 ± 0.27	<0.01

Values are presented as mean ± SD. cCSC, chronic central serous chorioretinopathy; RFPDT, reduced-fluence photodynamic therapy; BCVA, best-corrected visual acuity; logMAR, logarithmic minimum angle of resolution.

Table 4. Logistic regression analysis of good PDT response.

Covariate	Standardized coefficient (β)	P value
Hyperfluorescence on ICGA findings (Intense=1, Intermediate=2, No=3)	−0.267	0.012
Baseline BCVA (logMAR)	−0.110	0.298
T allele of *ARMS2* (rs10490924)	−0.217	0.039

ICGA, Indocyanine green angiography

DISCUSSION

In this study cohort of patients with cCSC, the *ARMS2* rs10490924 minor allele (T) was associated with poor response to RFPDT. To the best of our knowledge, this is the first report demonstrating that RFPDT response among patients with cCSC is influenced by genetic factors. Genetic screening may be useful for identifying patients with cCSC most likely to benefit from RFPDT.

Rijssen et al. [5] identified several clinical factors associated with RFPDT response among patients with CSC using the same outcome definitions (i.e., unsuccessful PDT defined as either incomplete SRF resolution within 2 months or post-treatment recurrence). Notably, the rates of unsuccessful PDT were similar to those in the present study (43.5% versus 39.1%), suggesting no clinically important differences in patient characteristics or treatment protocols. Although additional studies are required for validation, this similar overall treatment success suggests that the predictive efficacy of the rs10490924 genotype may be applicable to the general patient with cCSC population. The modest discrepancy in outcomes may be due to the larger sample size of the present study.

Haga et al. [4] reported that lower baseline BCVA and older age are associated with recurrent or persistent SRF among 79 cCSC-afflicted eyes treated with half-dose PDT and followed up for at least 3 years. Similarly, Rijssen et al. [5] found that older age and lower baseline BCVA as well as male sex are associated with SRF persistence or recurrence. In contrast, we found no differences in sex ratio, mean age, and baseline BCVA between the response groups. Although baseline visual acuity was marginally better in the good response group (p = 0.069), there was no statistically significant association between baseline visual acuity and the response to PDT treatment (p = 0.298). The influences of age and male sex should be evaluated in a larger-scale study controlling for baseline BCVA and the rs10490924 genotype.

The *ARMS2* rs10490924 SNP predicted the RFPDT response among patients with cCSC with relatively high statistical significance. Inoue et al. [8] reported that cCSC eyes without intense hyperfluorescence on ICGA are more likely to show recurrence. Consistent with the study by Inoue et al. [8], the logistic regression analysis in the present study showed that less intense hyperfluorescence on ICGA was statistically significantly associated with poor response to PDT treatment (p = 0.012). However, we did not find the association between the degree of hyperfluorescence on ICGA and the T allele of *ARMS 2* rs10490924 (p = 0.378). Yoneyama et al. [9] found that the major (G) allele of *ARMS2* rs10490924 is associated with choroidal vascular hyperpermeability (CVH) in patients with treatment-naïve polypoidal choroidal vasculopathy (PCV). This discrepancy may be due to ambiguous CVH findings and disease differences.

The mechanisms underlying reduced RFPDT response among carriers of the *ARMS2* rs10490924 T allele are currently a matter of speculation. The T allele is a known risk factor for age-related macular degeneration (AMD) [10] and is associated with poor visual acuity and recurrence in patients with PCV treated with PDT [11]. We also reported that *ARMS2* variants are associated with the 3-year BCVA outcome following PDT for wet AMD [12]. Sakurada et al. [13] reported to that the *ARMS2* rs10490924 genotype is associated with FA-measured lesion size in patients with PCV and that TT carriers have the greatest lesion size. Thus, the T allele may reduce the PDT outcome indirectly by exacerbating the clinical characteristics of cCSC other than ICGA findings rather than by influencing the PDT response directly.

The limitations of this study include the relatively small sample size, short follow-up period, and retrospective design. Further studies are required to elucidate the precise contributions of *ARMS2* variants to cCSC pathogenesis and PDT response. In conclusion, the degree of hyperfluorescence on ICGA and the *ARMS2* rs10490924 genotype are predictive of the response to RFPDT among patients with cCSC.

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REFERENCES

1. Daruich A, Matet A, Dirani A, Bousquet E, Zhao M, Farman N, Jaisser F, Behar-Cohen F. Central serous chorioretinopathy: Recent findings and new physiopathology hypothesis. Prog Retin Eye Res 2015; 48:82-118. [PMID: 26026923].
2. Chan WM, Lai TY, Lai RY, Liu DT, Lam DS. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. Ophthalmology 2008; 115:1756-65. [PMID: 18538401].
3. Liu HY, Yang CH, Yang CM, Ho TC, Lin CP, Hsieh YT. Half-dose Versus Half-time Photodynamic Therapy for Central Serous Chorioretinopathy. Am J Ophthalmol 2016; 167:57-64. [PMID: 27084002].
4. Haga F, Maruko R, Sato C, Kataoka K, Ito Y, Terasaki H. Long-term prognostic factors of chronic central serous chorioretinopathy after half-dose photodynamic therapy: A 3-year follow-up study. PLoS One 2017; 12:e0181479-[PMID: 28742138].
5. van Rijssen TJ, van Dijk EHC, Dijkman G, Boon CJF. Clinical characteristics of chronic central serous chorioretinopathy patients with insufficient response to reduced-settings photodynamic therapy. Graefes Arch Clin Exp Ophthalmol 2018; 256:1395-402. [PMID: 29732468].
6. Miki A, Kondo N, Yanagisawa S, Bessho H, Honda S, Negi A. Common variants in the complement factor H gene confer genetic susceptibility to central serous chorioretinopathy. Ophthalmology 2014; 121:1067-72. [PMID: 24365176].
7. de Jong EK, Breukink MB, Schellevis RL, Bakker B, Mohr JK, Fauser S, Keunen JE, Hoyng CB, den Hollander AI, Boon CJ. Chronic central serous chorioretinopathy is associated with genetic variants implicated in age-related macular degeneration. Ophthalmology 2015; 122:562-70. [PMID: 25439433].
8. Inoue R, Sawa M, Tsujikawa M, Gomi F. Association between the efficacy of photodynamic therapy and indocyanine green angiography findings for central serous chorioretinopathy. Am J Ophthalmol 2010; 149:441-6. [PMID: 20172070].
9. Yoneyama S, Sakurada Y, Kikushima W, Sugiyama A, Tanabe N, Mabuchi F, Kubota T, Iijima H. Genetic factors associated with choroidal vascular hyperpermeability and subfoveal choroidal thickness in polypoidal choroidal vasculopathy. Retina 2016; 36:1535-41. [PMID: 26745149].
10. 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. [PMID: 17692272].
11. 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. [PMID: 20671585].
12. Nakai S, Honda S. corresponding author Wataru Matsumiya, Akiko Miki, and Makoto Nakamura. ARMS2 variants may predict the 3-year outcome of photodynamic therapy for wet age-related macular degeneration. Mol Vis 2017; 23:514-9. [PMID: 28761324].
13. Sakurada Y, Kubota T, Imasawa M, Tsumura T, Mabuchi F, Tanabe N, Iijima H. Angiographic lesion size associated with LOC387715 A69S genotype in subfoveal polypoidal choroidal vasculopathy. Retina 2009; 29:1522-6. [PMID: 19898184].

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