Journal of Clinical & Experimental Ophthalmology
ISSN: 2155-9570

Bessho et al. J Clinic Experiment Ophthalmol 2011, 2:1
DOI: 10.4172/2155-9570.1000122

Research Article Open Access

Positive Association of *Complement Factor H* Gene Variants with the Effect of Photodynamic Therapy in Polypoidal Choroidal Vasculopathy

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Abstract

Purpose: To clarify the association of *complement factor H* (*CFH*) gene polymorphisms with the effects of photodynamic therapy (PDT) in polypoidal choroidal vasculopathy (PCV).

Methods: Ninety-three PCV subjects treated with PDT were recruited. Patients who showed anatomical success after the treatments with a single or two consecutive PDT sessions were classified as PDT responders. All others were classified as non-PDT responders. Three single nucleotide polymorphisms (SNPs), rs800292 (I62V), rs1061170 (Y402H) and rs1410996 were genotyped using the TaqMan assay.

Results: The genotype and allelic frequency of rs1061170 (Y402H) and rs1410996 were significantly different between PDT responders and non-responders. In these SNPs, the risk alleles for PCV prevalence were beneficial for PDT response. In the time course analysis, the cases with C/C genotype in rs1410996 showed a significant increase of mean visual acuity at 6 and 12 months after the first PDT.

Conclusions: The coding variants in *CFH* may be associated with the effects of PDT in PCV.

Introduction

Polypoidal choroidal vasculopathy (PCV) is a phenotype of age-related macular degeneration (AMD), a major cause of blindness in the elderly in industrial countries [1]. PCV accounts for 54.7% of patients with neovascular AMD in the Japanese population [2] and 24.5% in the Chinese population [3]. PCV has some characteristics such as orange-red protrusions at the posterior pole of the retina and distinct forms of choroidal vascular abnormalities, including vascular networks of choroidal origin with polypoidal lesions at their border found by indocyanine green angiography (ICG) [4,5]. PCV often shows spontaneous regression in its natural course, but on the other hand, it often causes severe hemorrhagic and exudative changes that result in a poor visual prognosis [5]. The clinical risk factors for a poor prognosis in PCV have been previously evaluated [5,6], but the molecular mechanisms responsible for the outcomes of the natural course or any interventions have not been reported yet.

PCV is known to have a better response to photodynamic therapy (PDT) than typical neovascular AMD, but the reason for this is not understood [7,8]. Moreover, there is some heterogeneity in the response to PDT among PCV patients [8,9]. Recently, genetic variants in the *complement factor H* (*CFH*) gene on chromosome 1q32 have been tested to explain the response to PDT [10-14]. In particular, the Y402H coding variant (rs1061170) in *CFH* is presumed to have functional consequences consistent with AMD pathology [15-19] and most studies have been conducted to find that *CFH* Y402H correlates with the outcome of PDT [10-14]. In neovascular AMD, Brantley et al. [12] reported an association of the *CFH* Y402H variant with the visual outcome after PDT [12]. However, other studies failed to demonstrate any association of this variant with the outcomes of PDT. Hence, more studies are needed to determine the role of *CFH* in the efficacy of PDT. In addition, we are interested in the association of *CFH* variants with the response to PDT in PCV cases, since PCV showed a poor association with *CFH* Y402H variants in the Japanese population [20].

In this study, 3 single nucleotide polymorphisms (SNPs) were genotyped, including rs800292 (I62V), rs 1061170 (Y402H) and non-coding SNP rs1410996, which are very representative of the common genetic variations in the *CFH* region including Asian populations, and the association between these *CFH* variants and the ability of PDT to regress PCV in a Japanese population was analyzed.

Materials and Methods

Study participants

This study was approved by the Institutional Review Board at the Kobe University Graduate School of Medicine, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects. All cases in this study were Japanese individuals recruited from the Department of Ophthalmology at the Kobe University Hospital in Japan.

All patients with PCV received ophthalmic examinations, including best-corrected visual acuity (BCVA) measurements, slit-lamp biomicroscopy of the fundi, color fundus photography, optical coherence tomography, fluorescein angiography (FA), and ICG. The visual acuities were determined using a Landolt C chart, and were converted to logarithm of the minimum angle of resolution (logMAR) values for calculation. All PCV subjects enrolled in the study met the criteria of definite cases of PCV as proposed by the Japanese Study Group of Polypoidal Choroidal Vasculopathy [21]. Briefly, ICG showed

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Received December 11, 2010; **Accepted** January 19, 2011; **Published** January 22, 2011

Citation: Bessho H, Honda S, Kondo N, Nishimura K, Negi A (2011) Positive Association of *Complement Factor H* Gene Variants with the Effect of Photodynamic Therapy in Polypoidal Choroidal Vasculopathy. J Clinic Experiment Ophthalmol 2:122. doi:10.4172/2155-9570.1000122

	PDT responder	PDT non-responder	p-value	
Age	73.1 ± 6.9	71.7 ± 7.9	0.41	†
Male/Female	55/12	20/6	0.57	*
GLD (μm)	3639 ± 1602	3959 ± 1624	0.39	†
Baseline BCVA logMAR	0.69 ± 0.33	0.60 ± 0.36	0.25	†
12M BCVA logMAR	0.51 ± 0.41	0.72 ± 0.39	0.028	†
BCVA change from baseline logMAR	-0.18 ± 0.37	0.12 ± 0.39	0.00098	†
No. of PDT performed (No. of eyes)	1 (46) 2 (22)§	1 (8) # 2 (12)## 3 (5) 4 (1)		
PDT frequency/year	1.3 ± 0.5	2.0 ± 0.8	0.000012	†

p-values are calculated by *X-square test or † two-tailed *t*-test
GLD; greatest linear dimension, BCVA; best-corrected visual acuity,logMAR; logarithm of minimum angle resolution, PDT; photodynamic therapy
§Six cases underwent additional PDT due to the development of recurrence or new lesion 5.5±2.0 months (mean±SD) after the complete regression with a single PDT
#the cases ceased for the second PDT due to the increase of euxdative changes after the first PDT
##the cases who declined further treatment due to no effect

Table 1: Data summary of the participants stratified by the response to photodynamic therapy in polypoidal choroidal vasculopathy.

Gene	SNP ID	Location	Major/Minor allele	Minor Allele Frequency		Association Results		
				Responder	Non-responder	Allelic OR (95%CI)	Allelic p-value	Corrected p-value*
CFH	rs800292	Exon 2 (I62V)	G/A	0.22	0.29	1.47 (0.71-3.03)	0.3	0.34
CFH	rs1061170	Exon 9 (Y402H)	T/C	0.13	0.02	7.69 (1.59-11.11)	0.026	0.026
CFH	rs1410996	Intron 14	C/T	0.25	0.42	2.17 (1.10-4.17)	0.024	0.032

*Corrections were performed with permutation test
SNP: single nucleotide polymorphism, CFH: complement factor H, OR: odds ratio, CI: coefficient interval

Table 2: Summary of single-SNP association analysis with the resopnse to photodynamic therapy in polypoidal choroidal vasculopathy.

			Genotype frequency						Association Results					
Gene	SNP ID	Major /Minor allele	Responder			Non-responder			Dominant model		Recessive model		Co dominant model	
			Major homo	Hetero	Minor homo	Major homo	Hetero	Minor homo	OR (95%CI)	P-value	OR (95%CI)	P-value	P-value	Corrected p-value*
CFH	rs800292	G/A	0.61	0.34	0.05	0.50	0.42	0.08	1.78 (0.28-11.30)	0.54	1.58 (0.63-3.93)	0.33	0.58	0.58
CFH	rs1061170	T/C	0.75	0.25	0.00	0.96	0.04	0.00	-	-	0.12 (0.015-0.94)	0.018	0.018	0.019
CFH	rs1410996	C/T	0.54	0.42	0.04	0.35	0.46	0.19	5.08 (1.12-23.08)	0.023	2.19 (0.86-5.62)	0.098	0.044	0.046

*Corrections were performed with permutation test
SNP: single nucleotide polymorphism, CFH: complement factor H, OR: odds ratio, CI: coefficient interval

Table 3: Summary of the genotype association analysis with the resopnse to photodynamic therapy in polypoidal choroidal vasculopathy.

a choroidal origin of the polypoidal lesions in all PCV cases, typically with vascular networks in the posterior poles on ICG and subretinal reddish-orange protrusions corresponding to the polypoidal lesions.

In this study, all patients underwent FA-guided full-dose PDT. The lesion status was assessed every three months, and treatments were performed again when serous retinal detachment or hemorrhage was recognized accompanied by a leakage on FA, or a defined lesion was observed on ICG. To analyze the effect of PDT, the consecutive PCV patients who underwent PDT monotherapy and followed-up at least for 12 months after the first session of PDT were included. No patient in this study received another treatment before PDT and during the follow-up period after PDT. The criteria to determine PDT responders versus non-responders are as follows. PCV patients who were successfully treated (complete resolution of the sub retinal fluid and hemorrhage with complete or partial disappearance of polypoidal lesions in angiography) with a single or two consecutive sessions of PDT were classified as PDT responders. All others were classified as PDT non-responders, which included the patients who underwent more than two sessions of PDT and who declined for further treatments due to no anatomical and visual improvement after two sessions of PDT. The 8 eyes of 8 patients that showed deteriorations of subretinal hemorrhage (more than 1 disc area) after the first PDT and paused the second session were included in non-responder group. In the PDT responders, 6 cases underwent additional PDT due to the development of recurrence or new lesion 5.5 ± 2.0 months (mean ± SD) after the complete regression with a single PDT. In the present study, we chose the anatomical success after PDT as a primary index to assess the response to PDT since it may better reflect the response to the treatment than BCVA. Since BCVA can be often maintained despite of sustained subretinal fluid for several months or it is often reduced due to excessive fibrotic scarring or atrophic changes of choroids that occur to varying degrees with a successful regression of the PCV lesions after PDT [22-24], we considered that it might be less suitable for scientific analysis. Anatomical resolution of the lesion means a successful occlusion of CNV tracts (or polypoidal lesions) with PDT, which consequently linked to the better BCVA after the treatment. Accordingly, the alteration of BCVA was chosen as a secondary index to be analyzed.

Genotyping

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

Statistical Analysis

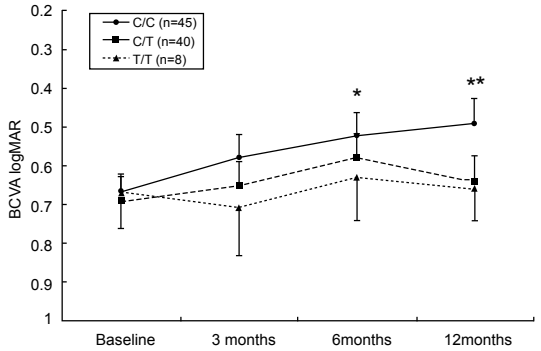
All SNPs were evaluated for the Hardy-Weinberg equilibrium using the χ^2 test (1 degree of freedom) with SNPAlyze version 7.0.1 (DYNACOM, Yokohama, Japan). The allelic and genotypic frequency distributions were compared between PDT responder and non-responder subjects using a χ^2 test with 1 or 2 degrees of freedom for the allelic and genotypic tests, respectively. For the time course analysis, two time points in each genotype were compared using a paired t-test (two-tail). P-values < 0.05 were considered statistically significant.

Results

The details of the pre- and post-treatment factors regarding PDT responders and non-responders are listed in Table 1. There was no difference in age, sex, GLD and baseline BCVA between PDT-responders and non-responders. However, the mean BCVA 12 months after the first PDT were significantly better in the PDT-responder group.

All SNPs reported in the present study did not show any significant deviations from the Hardy-Weinberg equilibrium over the entire sample (P > 0.001). Table 2 summarizes the minor allelic frequencies for all SNPs and the results from a single-SNP association study. The SNPs rs1061170 (Y402H) and rs1410996 were significantly associated with the proportion of PDT responders and non-responders. These associations were further supported by the genotypic analysis (Table 3), in which the most significant associations were found in the recessive models in rs1061170 (Y402H). To confirm the independence of these SNPs, the logistic regression analyses were added for all SNPs tested using SNPAlyze software. The results showed that the recessive model of rs1061170 was most significantly associated with the PDT response (p=0.0081), but the dominant model of rs1410996 also showed statistical significance (p= 0.011).

When comparing genotypes for alterations in the logMAR BCVA after PDT, the homozygous non-risk alleles in rs1410996 showed significant improvements in the logMAR BCVA at 6 and 12 months post-PDT, but heterozygous alleles or homozygous risk alleles showed no difference at 12 months after the initial PDT (Figure 1). The two genotypes in rs1061170 showed tendencies to improve the logMAR BCVA, although they were not statistically significant (Figure 2).



*p<0.01, **p<0.005

Figure 1: The influence of genotypes in rs1410996 on the time-course of logMAR BCVA value in all PCV patients treated by PDT. All values are presented as means±SEM.

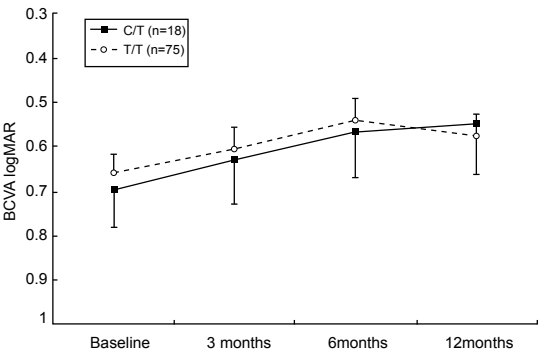


Figure 2: The influence of genotypes in rs1061170 on the time-course of logMAR BCVA value in all PCV patients treated by PDT. All values are presented as means±SEM.

Discussion

We genotyped 3 SNPs in the *CFH* region in PCV patients treated with PDT, and found that the SNPs rs1061170 (Y402H) and rs1410996 in the *CFH* region were significantly associated with a response to PDT.

Although the conclusions of previous reports regarding the association of *CFH* with the effects of PDT in neovascular AMD were contradictory [10-14], we found that coding variants in *CFH* were significantly associated with the response to PDT in PCV. This may be explained by differences in the phenotype (neovascular AMD vs PCV) or differences in the method of subgroup classification. Unlike many previous studies [10-14], we classified PDT responders and non-responders based on objective findings including fundus photography, FA and OCT. The classifications between "PDT-responder" and "non-responder" according with objective (anatomical) findings are also seen in recent publications [25,26].

Previous reports evaluated only *CFH* Y402H as a predictor for the outcome of PDT in neovascular AMD [10-14]. However, our results suggested that the association for the response to PDT was not only with Y402H, but also with rs1410996 in the *CFH* region. In particular, rs1410996 showed a significant association with both the proportion of PDT responders and non-responders, and with the visual outcome after PDT, whereas rs1061170 (Y402H) did not show any significant association with the visual outcome after PDT. It is interesting that variants in rs1410996 were reported to be associated with neovascular AMD and PCV, predominantly in Asian populations including Japanese [27-30]. Indeed, our previous study showed a possible association of the coding variants in rs1410996, rather than rs1061170, with susceptibility to PCV [20]. Since the minor allele frequency in rs1061170 is low (5-6%) in the Japanese population, [20,25,27,30] we hypothesized that it would be difficult to detect statistical significance with the limited number of subjects in that study. The present study, however, suggested an independent association of the coding variants in both rs1061170 and rs1410996 with the pathogenesis of PCV in terms of the effects of PDT. Although we could not detect significant association of rs1061170 (Y402H) with the alteration of BCVA after PDT possibly due to the lack of CC genotype in our cohort because of relatively smaller number of subjects, further study with larger population might address this issue.

Although the molecular mechanism by which *CFH* Y402H polymorphism contributes to the pathogenesis of neovascular AMD is under investigation [31], the mechanism by which coding variants in the *CFH* region contributes to PDT efficacy has not been addressed yet. Moreover, the biological basis of the association with rs1410996 is currently unknown, because the SNP does not reside in the coding sequence of *CFH*. Although the SNPs in this region could have non-coding effects on gene function, exhaustive re-sequencing of this locus is required to search for potentially undiscovered and more important causative variants. In the present study, however, it was noteworthy that both of the risk alleles in rs1061170 (C allele) and rs1410996 (C allele) for PCV turned out to be non-risk (beneficial) alleles for the response to PDT in PCV patients. Brantley et al [12] reported the beneficial effects of the C allele in rs1061170 (Y402H) for the visual outcome after PDT in neovascular AMD, although the reason was unknown [12]. Previous reports have demonstrated an association of the variants in another famous AMD susceptibility gene, *ARMS2/HTRA1*, with the lesion sizes of neovascular AMD and PCV [32-34]. However, they failed to demonstrate an association of the Y402H variants in *CFH*

with the lesion size in AMD or PCV [32]. Therefore, the initial lesion size, which may influence the response to PDT [8], was unlikely to be responsible for the outcome of PDT associated with the *CFH* variants. In fact, we did not find any difference in the initial GLD between PDT responders and non-responders in the present study. Accelerated inflammation due to CFH polymorphisms may have caused choroidal neovascularization in the pathogenesis of neovascular AMD and PCV, but it might also accelerate the embolization of neovascular tracts during PDT. The limitation of present study is relatively shorter follow-up period (12 months) after the treatment. Analysis for the outcome of PDT with longer follow-up period which reflects the recurrence rate and durability of the treatment [7] will be needed to disclose further association of CFH variants with the effect of PDT in the PCV patients.

Since PDT is known to induce a number of gene expression changes in the retina-choroidal complex [35], the detailed mechanisms by which multiple genes interact each other to close the choroidal neovascular tracts are poorly understood. However, the present genetic association study provides some clinical benefits which can be applied for personalized therapies in individual PCV patients.

Acknowledgement

This study was supported by a Grant-in Aid (C) 20592042 (SH) from the Ministry of Education, Science, and Culture, Tokyo, Japan. The funding organization had no role in the design or conduct of this research.

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