Biosketch

Sotaro Ooto MD, PhD, joined the Faculty of Medicine of Kyoto University and completed a medical course. He completed his residency in ophthalmology in 2001, after which he joined Kyoto University Graduate School of Medicine, where he worked on stem cell research. He became an assistant professor of Kyoto University Graduate School of Medicine in 2008, and he has been working as a member of the Macular Service and conducting studies on retinal imaging.

SUPPLEMENTAL TABLE. Reproducibility of the Determination of the Log Value of the Number of Reticular Pseudodrusen in the Macula Using Different Imaging Modalities

	Inter-observer Intraclass Correlation Coefficients		
Imaging	Center	Inner Ring[b]	Outer Ring[b]
Fundus photography[a]	0.946	0.839	0.845
IR	0.921	0.919	0.939
FAF	0.937	0.941	0.917

FAF = fundus autofluorescence; IR = infrared reflectance.

[a]Blue channel of fundus photography.

[b]Center, central fovea (1 mm); Inner ring, 1-3 mm from the central fovea; outer ring, 3-6 mm from the central fovea.

Vascular Endothelial Growth Factor Gene and the Response to Anti-Vascular Endothelial Growth Factor Treatment for Choroidal Neovascularization in High Myopia

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Purpose: To investigate the association between the *vascular endothelial growth factor (VEGF)* gene polymorphism and the response to anti-VEGF treatment for choroidal neovascularization (CNV) in highly myopic eyes.

Design: Retrospective cohort study.

Participants: A total of 357 unrelated highly myopic Japanese patients with axial lengths ≥26.0 mm in both eyes were eligible, and 83 patients who received anti-VEGF therapy for CNV and could be followed for more than 1 year were included.

Methods: We genotyped a functional single nucleotide polymorphism in the *VEGF* gene, rs2010963. The associations between the distribution of the rs2010963 genotype and the number of eyes with maintained or improved visual acuity (VA) were analyzed. Furthermore, multivariable logistic regression analysis was performed to adjust for 7 possible prognostic factors, including age, sex, CNV size, CNV location, administration of loading dose, pretreatment VA, and number of additional treatments.

Main Outcome Measures: The primary end point was maintenance of VA, and secondary end points were progression of chorioretinal atrophy (CRA) and recurrence of CNV.

Results: Mean age and mean axial length were not significantly different among 3 genotypes of rs2010963. The percentage of eyes with maintained or improved VA was significantly higher with the G allele of rs2010963 ($P = 0.016$), and stepwise analysis revealed that both rs2010963 and CNV size were associated with VA maintenance ($P = 0.040$ and 0.033, respectively). The secondary analysis revealed that administration of a loading dose was significantly associated with both CRA progression ($P = 0.031$) and recurrence of CNV ($P = 0.020$), whereas rs2010963 was not.

Conclusions: These results suggest that the *VEGF* polymorphism influences the VA prognosis in highly myopic eyes with CNV within 1 year after anti-VEGF treatment. This association was still observed after removing its confounding effect through CNV size. The rs2010963 polymorphism was not associated with CNV recurrence or CRA progression, which indicates that these changes are not tied to intrinsic factors and may be controllable by improving treatment methods. *Ophthalmology 2014;121:225-233 © 2014 by the American Academy of Ophthalmology.*

Myopia is the most common visual disorder in the world and a major public health concern, especially in East Asian populations. Its prevalence is estimated to be 25% in the United States and Western Europe and to be higher (40%–70%) in Asians.[1–5] Myopic eyes with very long axial lengths (≥26 mm) or a high degree of myopic refractive error (≤−6 diopters) are classified as high myopia.[6] In highly myopic eyes, choroidal atrophy and choroidal neovascularization (CNV) are the most vision-threatening complications.[7] Choroidal neovascularization mainly affects relatively younger adults aged 40 to 50 years,[8] and its natural history is extremely unfavorable. Visual acuity (VA) at 5 years after the onset of CNV decreases to ≤20/200 in 89% of the eyes and in 96% of the eyes after 10 years.[9] Because it is difficult to prevent the development of myopia and the occurrence of CNV, minimizing VA decline caused by CNV is of great importance for patients with high myopia.

Anti-vascular endothelial growth factor (VEGF) therapy has been used for the treatment of myopic CNV since 2005 and has shown good outcomes.[10–14] Visual acuity improves in many cases, but in some cases anti-VEGF therapy is ineffective. Several studies have been conducted to determine prognostic factors,[12,14,15] and we reported previously that smaller CNV size was a significant prognostic factor predicting better VA.[14]

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Recently, there has been a focus on genetic variants as a prognostic factor for the outcome of CNV treatment in both high myopia and age-related macular degeneration (AMD).[16–18] We reported that the *VEGF* polymorphism is associated with the response to intravitreal bevacizumab (IVB) and triple therapy for CNV secondary to AMD,[17] and that pigment epithelium-derived factor polymorphism is associated with the response of polypoidal choroidal vasculopathy to photodynamic therapy (PDT).[18] In the treatment of CNV secondary to high myopia, although Parmeggiani et al[19] evaluated the association between the genetic variants and the efficacy of PDT, no study has examined the association between the genetic variants and the response to anti-VEGF therapy. Because anti-VEGF therapy is becoming a first choice for treatment of myopic CNV,[20] it is important to evaluate the association between genetic variants and the response to anti-VEGF therapy, which could predict whether anti-VEGF therapy will be effective or not. Recently, we showed that the *VEGF* polymorphism is associated with the size of CNV secondary to high myopia, whereas it is not associated with the occurrence of CNV.[21] In the current study, we evaluated the associations between the *VEGF* polymorphism and the visual outcome after anti-VEGF treatment for CNV in highly myopic eyes.

Methods

All procedures in this study adhered to the tenets of the Declaration of Helsinki. The institutional review board and ethics committee of each institute involved approved the protocols of this study. All patients were fully informed of the purpose and procedures of this study, and written consent was obtained from each patient.

Patients and Methods

This is a retrospective study that reviewed the medical records of 357 patients with high myopia from whom genomic DNA had been extracted after obtaining informed consent; CNV was found in 158 patients. Patients who underwent anti-VEGF therapy and could be followed for at least 1 year were selected, and a total of 100 eyes were eligible for this study (inclusion/exclusion criteria are discussed later). Because genomic DNA from 17 patients was not available at the time of experiment, 83 patients were finally included in this study. All the patients were recruited from Kyoto University Hospital between September 2005 and April 2011. Each patient underwent a complete ophthalmic examination, including measurement of best-corrected visual acuity (BCVA), indirect ophthalmoscopy and slit-lamp biomicroscopy with a contact lens by a retina specialist, fluorescein angiography (FA) and indocyanine green angiography, and optical coherence tomography (OCT). The BCVA was measured with a Landolt chart and converted to a logarithm of the minimal angle of resolution for statistical analysis.

Inclusion criteria for this study were (1) an axial length of $\geq$26.00 mm or spherical equivalent refractive error of ≤ -6.0 diopters in phakic eyes; (2) fundus changes typical of pathologic myopia, such as chorioretinal atrophy (CRA), lacquer cracks, or atrophic patches; (3) FA documentation of CNV showing active leakage; and (4) follow-up period of at least 12 months after the first anti-VEGF treatment. The exclusion criteria were (1) history of intraocular surgery except for cataract surgery, (2) cataract surgery during the follow-up period, (3) previous anti-VEGF therapy, and (4) other ocular disease that can influence the BCVA, such as corneal opacity or myopic foveoschisis. If patients underwent bilateral anti-VEGF treatment, the eye treated earlier that fulfilled the criteria of this study was selected as the study eye for analysis.

Anti-Vascular Endothelial Growth Factor Therapy

The intravitreal dose of anti-VEGF was as follows: bevacizumab 1.25 mg, pegaptanib 0.3 mg, or ranibizumab 0.5 mg. All injections were performed under sterile conditions, and prophylactic topical antibiotics were applied from a few days before to 1 week after the injection. Anti-VEGF therapy was initiated by single injection or 3 monthly injections. After induction, ophthalmological examinations were performed at scheduled visits of 1-month intervals. Although most patients were examined every month for 1 year, some patients underwent scheduled examinations at 2- to 3-month intervals after resolution of exudative change. Repeat injection was recommended pro re nata on the basis of the judgment of the evaluating clinician. The re-injection criteria included any of the following findings: (1) persistence or recurrence of macular edema or serous retinal detachment in the OCT images, (2) persistence or recurrence of dye leakage in the FA images, (3) new subretinal hemorrhage from the myopic CNV, and (4) worsening of subjective symptoms, such as metamorphopsia, central scotoma, paracentral scotoma, or VA loss.

Genotyping

We genotyped one of the VEGF single nucleotide polymorphisms (SNPs), rs2010963, the C allele that we recently reported to be associated with larger myopic CNV.[21] This SNP has been shown to affect VEGF expression,[22] and its association with various diseases, such as AMD, diabetic retinopathy, Behçet's disease, Alzheimer's disease, and diabetes, has been evaluated.[23–32]

Genomic DNA was prepared from peripheral blood using a DNA extraction kit (QuickGene-610L, Fujifilm, Minato, Tokyo, Japan). Rs2010963 was genotyped using a TaqMan SNP assay with the ABI PRISM 7700 system (Applied Biosystems, Foster, CA). Deviations from the Hardy–Weinberg equilibrium (HWE) in genotype distributions were assessed using the HWE exact test.

Outcomes and Statistical Analysis

The primary end point of this study was VA maintenance from the baseline; we examined whether the patient's VA was the same or improved by a Landolt chart at the visit 1 year after the first anti-VEGF treatment. For the secondary end points, we evaluated the recurrence of CNV and CRA progression. The progression of CRA was judged according to our previous report.[33] Briefly, 2 of the authors (A.O. and K.Y.) judged color fundus photographs as a binary trait based on changes in patchy atrophy. When the 2 authors disagreed, a third author (A.T.) was asked to arbitrate. The association of these conditions with the rs2010963 genotype was analyzed using the Cochran–Armitage test.

To specifically evaluate the contribution of the rs2010963 SNPs to the end points, we performed multivariable logistic regression analysis to adjust for age, sex, and previously reported prognostic factors, such as CNV size, pretreatment VA, CNV location, initial loading dose, and number of additional anti-VEGF drug injections after the initial single or 3 monthly injection treatments.[13,14] The location of CNV, subfoveal or not, was treated as a binary trait. After fitting a full model, we selected variables by a stepwise method. When analyzing the association with recurrence, we did not use the number of treatments as a possible predictive factor,

Table 1. Patient Characteristics

Variable	Value
Total (n)	83
Mean age (yrs ± SD)	64.5±11.2
Sex (male:female)	18:65
Mean axial length (mm ± SD)	29.00±1.60
Mean pretreatment BCVA (logMAR)	0.65±0.42
CNV location	
Subfoveal (n, %)	62 (74.7%)
Juxtafoveal (n, %)	18 (21.7%)
Extrafoveal (n, %)	3 (3.6%)
History of other treatment	
None	73
PDT	9
Triamcinolone acetonide	1
Drug	
Bevacizumab	61
Ranibizumab	20
Pegaptanib	2
CNV size (mm^2)	
Mean ± SD	0.93±0.83
Range	0.05–3.43
Greatest linear dimension (mm)	
Mean ± SD	1383±687
Range	390–3370

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; logMAR = logarithm of the minimum angle of resolution; PDT = photodynamic therapy; SD = standard deviation.

because a high number of treatments was probably a consequence of recurrence, not the cause of recurrence.

The differences in basic demographics among 3 genotype groups were analyzed by appropriate statistical tests using analysis of variance, Fisher exact test, or linear regression analysis. Tukey–Kramer test for post hoc was performed as needed. These analyses were performed using Software R (R Foundation for Statistical Computing, Vienna, Austria) and PLINK version 1.07 (available at: http://pngu.mgh.harvard.edu/w purcell/plink/index, accessed February 18, 2012). A P value < 0.05 was considered statistically significant.

Results

There were 83 patients with CNV in highly myopic eyes who underwent treatment with bevacizumab (62 eyes), pegaptanib (3 eyes), or ranibizumab (18 eyes). All patients were followed for at least 12 months. Anti-VEGF therapy was initiated by a single injection in 65 eyes (initial loading dose [−] group) and by 3 monthly injections in the other 18 eyes (initial loading dose [+] group). Demographic information and characterization of the patients are shown in Table 1. The CNV was subfoveal in 73.5% of patients, and 88.0% of patients were treatment-naïve. During the follow-up period, individuals received a mean of 1.1 additional injections.

Table 2 describes the demographics and clinical phenotypes of the study population according to rs2010963 genotype. The genotype distribution was CC:CG:GG = 16:34:27. The genotype distribution was in HWE (P = 0.403). There were no differences in age, sex, or axial length in the 3 genotype groups. The number of additional anti-VEGF injections within 1 year showed significant differences (P = 0.036) and was significantly higher in patients with the CC genotype compared with those with CG and GG genotypes (P = 0.045 and 0.049, respectively, with Tukey–Kramer multiple comparison). Likewise, the greatest linear dimension and CNV size were relatively larger in patients with the CC genotype (P = 0.10). Although this association was not statistically significant, this trend was compatible with our previous report showing that CNV size in highly myopic eyes is larger in patients with the rs2010963 CC genotype than in those with the CG and GG genotypes.[21]

The VA outcome also showed a similar association to the VEGF genotype. Figure 1 shows VA improvement from the baseline according to rs2010963 genotype. Eyes with the CC genotype had worse VA outcomes than eyes with the GG or CG genotypes. Although retinal exudative change disappeared after anti-VEGF treatment in patients with CC genotype (Fig 2), only half of the patients with the CC genotype of rs2010963 had maintained VA 1 year after the first injection, whereas more than 80% of patients with the CG or GG genotype (Fig 3) maintained VA. The

Table 2. Clinical Phenotypes of Myopic Patients with Choroidal Neovascularization by rs2010963 Genotype

Characteristics	CC	CG	GG	P Value*
No. of patients (n, %)	16 (19.3%)	34 (41.0%)	27 (32.5%)	
Mean age (yrs ± SD)	66.2±11.8	64.8±10.4	61.5±12.0	0.36
Male:female	4:12	6:28	8:19	0.54†
Mean axial length (mm ± SD)	29.42±1.76	29.07±1.29	28.84±1.88	0.53
Subfoveal CNV (n, %)	14 (87.5%)	24 (70.6%)	19 (70.3%)	0.42
No. of treatments (per 12 mos)	2.81	1.91	1.89	0.036
Presence of loading dose (n, %)	5 (31.3%)	8 (23.5%)	4 (14.8%)	0.20
Pretreatment VA (logMAR)	0.62±0.35	0.64±0.47	0.70±0.44	0.80
Greatest linear dimension (mm)	1651±879	1195±529	1498±732	0.063/0.10‡
CNV size (mm^2)	1.26±1.08	0.76±0.78	0.99±0.76	0.15/0.10‡
Maintenance of VA (n, %)	8 (50.0%)	28 (82.3%)	23 (85.2%)	0.016§
Recurrence in 1 yr (n, %)	9 (56.3%)	7 (20.6%)	12 (44.4%)	0.75§
CRA progression in 1 yr (n, %)	10 (62.5%)	12 (35.2%)	14 (51.9%)	0.73§

CNV = choroidal neovascularization; CRA = chorioretinal atrophy; logMAR = logarithm of the minimal angle of resolution; SD = standard deviation; VA = visual acuity.
*Analysis of variance.
†2×3 Fisher exact test.
‡Recessive model.
§Cochran–Armitage test.

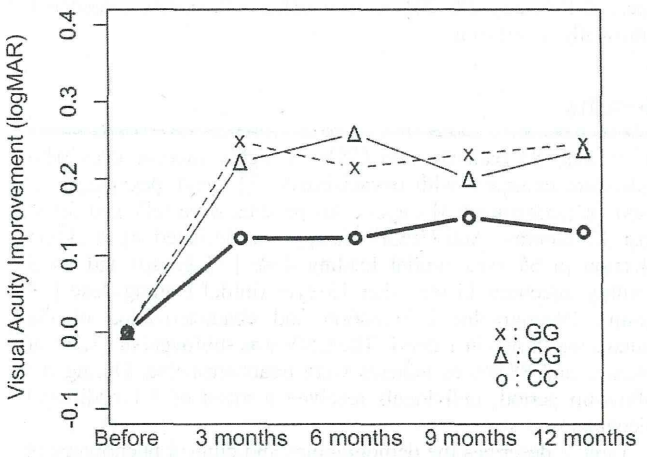

Figure 1. Improvement in visual acuity (VA) according to rs2010963 genotype. Change in VA in logarithm of the minimum angle of resolution from baseline of eyes with the GG, CG, and CC genotypes is plotted at each time point. The VA time course was signi□cantly worse in eyes with the CC genotype than the CG or GG genotype. logMAR = logarithm of the minimum angle of resolution.

statistical analysis revealed a significant association between the rs2010963 genotype and the rate of VA maintenance (Table 2, $P = 0.016$). The association was also significant when evaluated with treatment-naïve patients only ($P = 0.032$) and when evaluated with only patients with subfoveal CNV ($P = 0.041$). As for the secondary end points, recurrence rate and CRA progression within 1 year were not associated with rs2010963 genotype ($P = 0.75$ and 0.73, respectively).

The results of the multivariable logistic regression for maintenance of VA are shown in Table 3. Of 8 prognostic factors, the G allele of rs2010963 ($P = 0.047$), pretreatment VA ($P = 0.025$), and CNV size ($P = 0.015$) showed a significant association with the maintenance of VA; odds ratios (ORs) were 2.51, 9.79, and 0.35, respectively. To find the best-fit model, we analyzed the associations with a stepwise method. Vascular endothelial growth factor rs2010963 G allele gave patients a 2.3 times higher tendency to have maintained VA after anti-VEGF treatment ($P = 0.040$).

To ensure that the initial treatment method did not affect the genotype–phenotype associations between rs2010963 and VA outcome, we performed 2 analyses. First, we compared the patients' characteristics between the single initial treatment group and the 3 monthly injection group (Table 4). There was no difference in genotype of rs2010963 ($P = 0.19$). The VA was maintained in 78.5% of eyes without an initial loading dose and in 77.8% of eyes with an initial loading dose ($P = 1.0$). Although patients who underwent an initial loading dose were significantly older than those who did not ($P = 0.014$), there were no statistically significant differences in sex ($P = 0.22$), axial length ($P = 0.19$), pretreatment VA ($P = 0.67$), or greatest linear dimension ($P = 0.26$). Second, we performed logistic regression analysis using only eyes treated with a single initial treatment (Table 5). This analysis revealed a more significant association of rs2010963 genotype with VA maintenance ($P = 0.0080$). In addition to the smaller CNV size ($P = 0.0039$), younger age ($P = 0.040$) was also a positive predictive factor for VA maintenance.

Finally, we explored factors associated with the recurrence rate of CNV and CRA progression by stepwise analysis (Table 6). The analysis did not select the rs2010963 genotype as a prognostic factor for recurrence and CRA progression within 1 year. Among the 7 factors evaluated, the prognostic factors of recurrence were advanced age (OR, 1.07; $P = 0.013$) and presence of loading dose (OR, 0.21; $P = 0.031$). The presence of a loading dose also showed a significant association with CRA progression (OR, 4.15; $P = 0.020$).

Discussion

In the present study, we demonstrated a significant association between the VEGF rs2010963 genotype and the maintenance of vision after treatment for CNV with anti-VEGF therapy in highly myopic eyes. Parmeggiani et al[19] also evaluated the genetic association for response to myopic CNV treatment. They showed a significant association between 2 genes and CNV responsiveness to PDT. Although the results gave us clinically important information, anti-VEGF therapy is now becoming the first choice for the treatment of CNV in high myopia because of its efficacy and safety.[20] Our findings of the associations between VEGF gene polymorphism and the response to anti-VEGF treatment for CNV in highly myopic eyes in the present study will give us important insight into today's treatment for myopic CNV.

Genetic associations with myopia have been investigated for several decades. Although we reported 2 susceptible loci for high myopia using genome-wide association studies[34,35] and reproduced the association of recently reported myopia susceptibility loci on chromosome 15,[36] susceptibility genes for myopia have not been identified, and it is still difficult to find the means to prevent myopia. Thus, in the clinical setting, controlling not high myopia but its complications is currently the more practical approach. Recently, we reported that the VEGF polymorphism affects the size of myopic CNV, whereas it is not associated with its occurrence. Patients with the C allele of rs2010963 had significantly larger CNV.[21] It has been reported that larger myopic CNV size is a predictive factor for poor outcomes of anti-VEGF treatment.[12–14] Considered together, it would be reasonable to suggest that VEGF polymorphism affects the response to anti-VEGF therapy for CNV in highly myopic eyes. In the current study, however, we showed that both CNV size and VEGF genotype were associated with VA maintenance, even after multivariable logistic regression analysis. The VEGF genotype affected the visual outcome regardless of its effect on the CNV size.

Only 50% of the patients who had the CC genotype of VEGF rs2010963 maintained their VA after anti-VEGF treatment, whereas 80% of the patients with the CG or GG genotype maintained their VA. Because retinal exudative change itself was resolved in all cases after treatment, retinal damage caused by CNV might be different depending on the genotype, and CNV with the C allele might be more harmful to retinal cells. Another possibility is that the potency of the anti-VEGF treatment might be affected depending on the genotype. As shown in Figure 2, some patients still had exudative change 1 week after anti-VEGF treatment, whereas the exudative changes were completely resolved 1 to 3 months after the treatment. Rapid disappearance of retinal exudative change in patients with

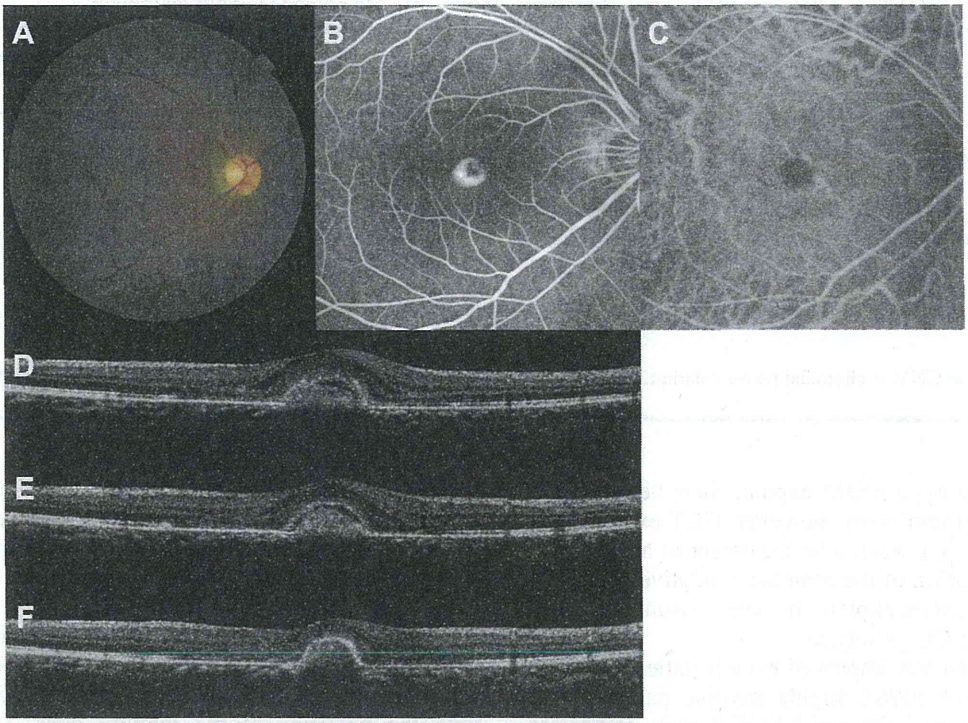

Figure 2. **(A)** Color fundus photograph, **(B)** fluorescein angiography (FA), **(C)** indocyanine green angiograph, and **(D–F)** spectral-domain optical coherence tomography (OCT) images of a patient who received intravitreal bevacizumab (IVB). This 42-year-old woman with choroidal neovascularization (CNV) in her highly myopic right eye had the rs2010963 CC genotype. **(A)** Pretreatment color fundus photograph, **(B)** pretreatment FA, and **(C)** pretreatment indocyanine green angiograph showed CNV beneath the fovea. **(D)** Pretreatment OCT image showed retinal exudative change. **(E)** Exudative change was still present 1 week after IVB and **(F)** almost resolved 1 month after IVB. Decimal VA was improved from 0.4 (pretreatment) to 0.7 (1 week after treatment), 0.7 (3 months after treatment), and 1.2 (1 year after treatment).

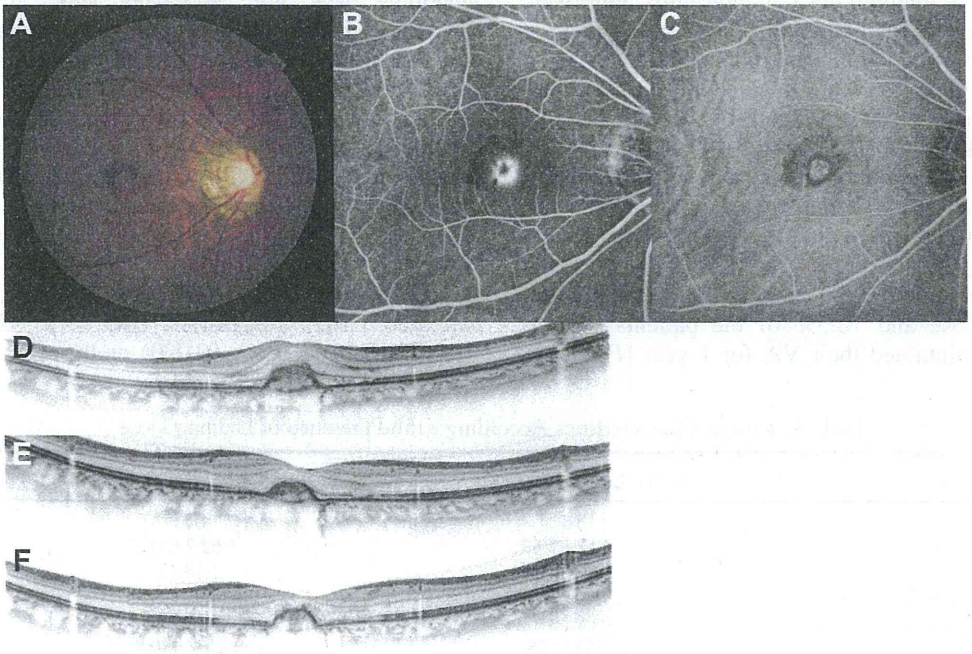

Figure 3. **(A)** Color fundus photograph, **(B)** fluorescein angiography (FA), **(C)** indocyanine green angiograph, and **(D–F)** spectral-domain optical coherence tomography (OCT) images of a patient who received intravitreal bevacizumab (IVB). This 36-year-old man with choroidal neovascularization (CNV) in his highly myopic right eye had the rs2010963 GG genotype. **(A)** Pretreatment color fundus photograph, **(B)** pretreatment FA, and **(C)** pretreatment indocyanine green angiograph showed CNV beneath the fovea. **(D)** Pretreatment OCT image showed retinal exudative change. **(E)** Exudative change almost resolved 1 week after IVB and **(F)** resolved 1 month after IVB. Decimal visual acuity (VA) was improved from 0.4 (pretreatment) to 0.7 (1 week after treatment), 0.8 (3 months after treatment), and 1.5 (1 year after treatment).

Table 3. Multivariable Logistic Regression Analysis for Maintenance of Visual Acuity

	Full Model			Stepwise Method		
	OR	95% CI	P Value	OR	95% CI	P Value
rs2010963 G allele	2.51	1.05–6.64	0.047	2.30	1.06–5.34	0.040
Pretreatment VA (logMAR)	9.79	1.60–93.2	0.025	4.17	0.95–23.8	0.077
CNV size	0.35	0.14–0.78	0.015	0.48	0.23–0.92	0.033
Presence of loading dose	4.15	0.84–28.1	0.10		Not included	
No. of additional treatments	1.38	0.75–2.78	0.33		Not included	
Subfoveal CNV	0.46	0.07–2.28	0.36		Not included	
Age	0.95	0.89–1.01	0.15		Not included	
Sex	0.89	0.19–3.68	0.88		Not included	

CI = con□dence interval; CNV = choroidal neovascularization; logMAR = logarithm of the minimal angle of resolution; OR = odds ratio; VA = visual acuity.

the CG or GG genotype might explain their better visual prognosis. In the current study, however, OCT examination was not performed at 1 week after treatment in all patients. Thus, further evaluation of the remnant exudative change at an early time point might explain the worse visual outcomes in patients with the CC genotype.

Because the mean VA improved even if patients had the CC genotype of rs2010963, highly myopic patients with CNV should be treated with anti-VEGF therapy regardless of their rs2010963 genotype. However, if we examine patients' genotype before treatment, we can predict their visual outcome after anti-VEGF treatment. Furthermore, when new treatments are developed, genotype knowledge would lead to more accurate information of their treatment option.

The need for a loading dose is presently controversial.[37,38] When patients treated with an initial loading dose of 3 monthly injections and patients treated with a single initial injection were evaluated together, our multivariable logistic regression analysis showed that the presence of loading dose was not associated with VA maintenance. Furthermore, the patients' characteristics were not significantly different between patients with a loading dose and patients without a loading dose except for their age. The rs2010963 genotype distribution was not significantly different ($P = 0.19$), and 77.8% of the patients with a loading dose and 78.5% of the patients without a loading dose maintained their VA for 1 year ($P = 1.0$), suggesting that loading dose did not affect our findings of the association between rs2010963 and visual outcome of anti-VEGF treatment for CNV in high myopia. In addition to this analysis, we performed a subanalysis using cases without a loading dose only. This analysis also showed that rs2010963 was significantly associated with the visual outcome ($P = 0.008$). However, both CNV recurrence and CRA progression were associated with the presence of the loading dose. Patients treated with 3 monthly injections showed lower recurrence and more CRA progression when evaluated with stepwise multivariable logistic regression analysis. Although our retrospective study cannot conclude whether treatment method affects recurrence of CNV and CRA progression, considered together with the finding that rs2010963 genotype was not associated with these secondary outcomes, it might be suggested that recurrence of CNV and CRA progression is affected by the method of treatment rather than an intrinsic factor such as genotype.

Uemoto et al[39] have retrospectively reviewed 27 eyes of myopic patients with CNV who underwent IVB treatment and reported that the CNV size, number of treatments, and duration of follow-up were associated with enlargement of CRA. In our study, CNV size was not selected among the factors associated with CRA progression by stepwise analysis, but patients treated with 3 monthly injections showed increased CRA progression (OR, 4.15; 95% confidence interval, 1.31–15.0; $P = 0.020$), and the number of additional

Table 4. Patient Characteristics According to the Presence of Loading Dose

Characteristics	Initial Loading Dose (+)	Initial Loading Dose (−)	P Value
No. of patients	18	65	
Mean age (yrs ± SD)	69.2±7.59	63.2±11.7	0.014
Male:female	2:16	18:47	0.22
Mean axial length (mm ± SD)	29.44±1.56	28.88±1.60	0.19
Pretreatment VA (logMAR)	0.69±0.44	0.64±0.42	0.67
Greatest linear dimension (mm)	1553±708	1336±680	0.26
Maintenance of VA (n, %)	14 (77.8%)	51 (78.5%)	1.00
Rs2010963 genotype (CC:CG:GG)	5:8:4	11:26:23	0.19*

logMAR = logarithm of the minimal angle of resolution; SD = standard deviation; VA = visual acuity.
*Chi-square test for trend.

Table 5. Multivariable Logistic Regression Analysis for Maintenance of Visual Acuity Using Only Eyes Treated with Single Initial Treatment

	Full Model			Stepwise Method		
	OR	*95% CI*	*P Value*	*OR*	*95% CI*	*P Value*
rs2010963 G allele	11.8	2.42–113	0.0093	11.4	2.46–103	0.0080
Pretreatment VA (logMAR)	14.5	1.38–311	0.048	11.8	1.27–210	0.052
CNV size	0.044	0.0032–0.26	0.0048	0.043	0.0032–0.24	0.0039
Presence of loading dose		Not valid			Not valid	
No. of additional treatments	3.71	1.20–20.1	0.064	3.52	1.22–17.9	0.060
Subfoveal CNV	0.80	0.09–6.40	0.83		Not included	
Age	0.90	0.81–0.98	0.034	0.91	0.82–0.99	0.040
Sex	0.49	0.05–3.32	0.49		Not included	

CI = confidence interval; CNV = choroidal neovascularization; logMAR = logarithm of the minimal angle of resolution; OR = odds ratio; VA = visual acuity.

treatments showed a marginal association (OR, 1.63; 95% confidence interval, 1.00–2.86; $P = 0.062$). More treatment would cause more CRA progression. In contrast, in our previous study that evaluated CRA progression of 22 eyes with myopic CNV for 4 years after IVB, there was not an association between the number of treatments and the CRA progression.[33] Because CRA enlarges in as many as 70% to 80% of patients with myopic CNV when followed for more than 2 years,[13,33] the treatment method would not affect long-term CRA progression.

Study Limitations

The largest limitations are the study's retrospective design and small sample size. However, the patient demographics are similar to previous reports, and it is likely our subjects are representative of the general population with this disease. Furthermore, the results are believable, because most previously reported prognostic factors are found again in our final model that predicts prognosis. Third, we included both treatment-naive patients and patients with previous treatment. Furthermore, we included patients treated with bevacizumab, pegaptanib, or ranibizumab. Although the association of rs2010963 genotype with maintenance of VA also was significant when evaluated with treatment-naïve patients ($P = 0.032$), the influence of such a difference should be further explored. Fourth, we cannot differentiate CRA progression that resulted from CNV regression, high myopia itself, or previous PDT. However, to reduce the influence of CRA due to high myopia, we judged CRA to be progressing only when CRAs were adjacent to the original CNV location. Furthermore, to eliminate the influence of previous PDT, we also conducted the same analysis using treatment-naive patients (Table 7, available at http://aaojournal.org). This analysis still showed a significant association between the CRA progression and the number of additional treatments ($P = 0.043$). Fifth, this is not a comparative study of the untreated patients with CNV. Thus, there remains the possibility that the worse VA outcome is due to its natural course.

In conclusion, we have shown that the VEGF rs2010963 genotype itself is a significant prognostic factor for visual outcome within 1 year after anti-VEGF treatment for CNV in high myopia, even after removing its confounding effect through CNV size. Choroidal neovascularization recurrence and CRA progression were not associated with the rs2010963 genotype but were associated with the mode of treatment. Understanding of both intrinsic and extrinsic factors associated with visual outcomes, CNV recurrence, and CRA progression will help to improve management strategies for high myopia.

Table 6. Stepwise Multivariable Logistic Regression Analysis for Secondary End Points

	Recurrence within 1 Year			CRA Progression after 1 Year		
	OR	*95% CI*	*P Value*	*OR*	*95% CI*	*P Value*
rs2010963 G allele		Not included			Not included	
Pretreatment VA (logMAR)	0.29	0.063–1.16	0.094		Not included	
CNV size	1.98	0.98–4.29	0.065		Not included	
Presence of loading dose	0.21	0.045–0.80	0.031	4.15	1.31–15.0	0.020
No. of additional treatments		Not employed		1.63	1.00–2.86	0.062
Subfoveal CNV	3.57	0.97–15.6	0.068		Not included	
Age	1.07	1.02–1.14	0.013		Not included	
Sex		Not included			Not included	

CNV = choroidal neovascularization; CRA = chorioretinal atrophy; logMAR = logarithm of the minimal angle of resolution; OR = odds ratio; VA = visual acuity.

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