

# VEGFR2 Gene Polymorphisms and Response to Anti-Vascular Endothelial Growth Factor Therapy in Age-Related Macular Degeneration

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**Purpose:** A previously published study demonstrated a pharmacogenetic association between the minor alleles of 2 *VEGFR2* single nucleotide polymorphisms (SNPs) and greater improvement in visual acuity (VA) to treatment with ranibizumab, an anti-vascular endothelial growth factor (VEGF) drug, in patients with neovascular age-related macular degeneration (AMD). We evaluated whether this association was replicated among patients who participated in the Comparison of AMD Treatments Trials (CATT) or the Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation (IVAN) trial.

**Design:** Cohort studies within randomized clinical trials.

**Participants:** Eight hundred thirty-five patients participating in CATT and 512 patients participating in IVAN.

**Methods:** Each patient was genotyped for the SNPs rs4576072 and rs6828477 in the *VEGFR2* gene.

**Main Outcomes Measures:** Mean change in VA from baseline to 1 year after initiation of treatment with ranibizumab or bevacizumab. Differences in VA response between the patient group homozygous for the minor allele of each SNP and the other genotype groups were evaluated with analysis of variance. Differences in VA response by the number of minor alleles present for either SNP or both combined were evaluated with tests of linear trend. Analyses were conducted separately for CATT and IVAN participants and with both the studies combined.

**Results:** No statistically significant difference in mean change in VA was identified between genotypes of either SNP ( $P \geq 0.05$ ). Furthermore, a stepwise analysis failed to show a significant interaction for either SNP based on the number of minor alleles present. The lack of association was similar in both the CATT and IVAN cohorts and whether the analysis combined patients treated with either ranibizumab or bevacizumab or when restricted to patients treated with ranibizumab only.

**Conclusions:** The CATT and IVAN data do not support a pharmacogenetic association between the 2 *VEGFR2* SNPs, rs4576072 and rs6828477, and change in VA in response to anti-VEGF therapy in patients with neovascular AMD. *Ophthalmology* 2015;122:1563-1568 © 2015 by the American Academy of Ophthalmology.

Treatments based on inhibiting the activity of vascular endothelial growth factor (VEGF) have transformed the care of patients with neovascular age-related macular degeneration (AMD). In neovascular AMD, choroidal neovascularization invades the subretinal space, resulting in exudation of fluid, subretinal hemorrhage, and severe visual loss. The 3 commonly used anti-VEGF drugs are bevacizumab, ranibizumab, and aflibercept. All 3 drugs are highly effective and provide similar functional outcomes.<sup>1-3</sup> However, despite this remarkable clinical effect, there is a wide range of treatment responses.<sup>1,2</sup> Because genetic variation has been shown to influence strongly the development and progression of neovascular AMD, attention has been focused on the influence of genetic risk alleles on treatment response to anti-VEGF therapy. Initial studies

have suggested that the major risk alleles for the development of AMD do not affect response to therapy in patients with neovascular AMD.<sup>4,5</sup>

Vascular endothelial growth factor A is the primary angiogenic factor involved in the development of choroidal neovascularization. Because anti-VEGF therapeutics bind VEGF-A and its isoforms, it is biologically plausible that single nucleotide polymorphisms (SNPs) that regulate VEGF-A expression also could be involved in modulating the response to anti-VEGF drugs. Our recent study of 8 SNPs within *VEGFA* and *VEGFR2* revealed no association between these polymorphisms and treatment response.<sup>6</sup> However, a recent study by Hermann et al<sup>7</sup> evaluated the association of 126 SNPs in *VEGF* genes and their receptors (*VEGFR*) with response to ranibizumab in a case

series of 366 patients with neovascular AMD. In an analysis that did not account for multiple comparisons, the minor alleles of 2 SNPs (rs4576072 and rs6828477) in *VEGFR2*, the gene encoding the receptor responsible for mediating most cellular responses to VEGF, were associated independently with a greater improvement in visual acuity (VA). At 1 year, the presence of the minor allele at either SNP was associated with 1 to 2 lines of VA improvement compared with those patients without the minor allele. Furthermore, improvement was reported as additionally increased for each SNP with the presence of an additional minor allele.

The Comparison of AMD Treatments Trials (CATT) and the Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation (IVAN) trial are 2 large, multicenter, randomized clinical trials that compared bevacizumab and ranibizumab in patients with neovascular AMD. Genetic assessment of participants in these trials provides an ideal opportunity to investigate pharmacogenetic associations, given that all outcomes were determined in the context of a prospective randomized clinical trial using well-defined protocols. In an effort to verify the pharmacogenetic association between *VEGFR2* SNPs and response to anti-VEGF therapy, we evaluated the 2 SNPs (rs4576072 and rs6828477) in participants from the CATT and IVAN trials.

## Methods

### Comparison of Age-Related Macular Degeneration Treatments Trials Participants

Study procedures for CATT have been reported previously and are provided on [Clinicaltrials.gov](http://Clinicaltrials.gov) (identifier, NCT00593450).<sup>1</sup> Written informed consent was obtained from all CATT study participants involved in the genetics ancillary study. Institutional review board approval was obtained by the Cleveland Clinic and all participating CATT centers. We recruited 835 CATT participants for the genetics study, and details about this cohort are well documented elsewhere.<sup>4,6</sup> All analyses investigating the effect of genotype on response to treatment for this study were evaluated with outcomes data at 1 year to minimize confounding factors that may occur at later time points in the trial. Furthermore, most of the response in morphologic and visual outcomes occurred within the first 6 months of treatment.<sup>1</sup> Finally, we chose to look at 1-year outcomes so that we could compare our results directly with those of Hermann et al.<sup>7</sup>

### Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularisation

Study procedures for IVAN have been reported previously and are provided on [Controlled-trials.com](http://Controlled-trials.com) (identifier, ISRCTN92166560).<sup>2</sup> Informed consent for participating in this additional genetics study was obtained from all IVAN genetic study participants. A United Kingdom National Health Service Research Ethics Committee gave approval (reference, 07/NIR03/37). The IVAN study investigators recruited 512 IVAN patients for the genetics study, and details about this cohort are well documented elsewhere.<sup>5</sup> Similar to the CATT analyses, this analysis of the IVAN data focused on 1-year outcomes.

## Genotype Determination

In CATT, approximately 10 to 20 ml of peripheral blood were collected from each patient. DNA was extracted and purified from leukocytes as previously described.<sup>4</sup> Two SNPs in *VEGFR2* (rs4576072 and rs6828477) were evaluated in each patient. Genotyping was performed using TaqMan SNP genotyping assays (Applied Biosystems, Grand Island, NY) as described previously.<sup>4</sup> All laboratory personnel were masked to treatment assignment and patient clinical data. For the genetic analysis of IVAN samples, DNA was extracted and normalized from 10 ml of peripheral blood using an established method.<sup>8</sup> The SNP assays were performed using KASPar (KBioscience Competitive Allele-Specific Polymerase chain reaction assay) biochemistry as previously described.<sup>5</sup>

## Measures of Response to Treatment

For the purposes of this study, the main outcome measure of responsiveness to treatment was defined as the mean change in best-corrected VA from baseline at 1 year in study eyes. In both CATT and IVAN, VA examiners were masked to treatment status and best-corrected acuity obtained at every visit in study eyes. Acuity was measured using either electronic VA charts (CATT) or backlit early treatment diabetic retinopathy charts (IVAN). Regardless of the method of acuity testing, the measure of acuity was Early Treatment Diabetic Retinopathy Study letters read in both of the clinical trials, thereby allowing easy pooling of data for analysis.

## Statistical Analysis

The mean VA change from baseline at 1 year was compared among all 3 genotype groups (TT, CT, CC) for each SNP using the linear trend test. Following the same analysis approach used by Hermann et al.,<sup>7</sup> 3 genotype groups (CC, CT, and CC or CT) having a minor C allele were compared with the genotype TT using analysis of variance. This analysis was performed among patients treated with either ranibizumab or bevacizumab and among patients treated with ranibizumab only. Data from the CATT and IVAN studies were considered separately and in a combined analysis controlling for the study. An uncorrected *P* value less than 0.025 was considered statistically significant after applying the Bonferroni adjustment to account for the evaluation of 2 SNPs; no further adjustments were made for multiple statistical tests for each SNP or for subgroup analyses.

## Results

We evaluated a total of 1347 patients with neovascular AMD across 2 SNPs within the *VEGFR2* gene reported previously to have a significant influence on the treatment response to ranibizumab. The minor allele frequencies for both SNPs were nearly identical in the 835 CATT participants, in the 512 IVAN participants, and in the Hermann et al.<sup>7</sup> cohort (0.43, 0.42, 0.40, respectively, for rs6828477; 0.16, 0.16, 0.16, respectively, for rs4576072; Table 1).

Among CATT participants, there was no significant difference in mean change in VA at 1 year between patients homozygous for the C allele (minor allele) for either of the 2 *VEGFR2* SNPs of interest (rs4576072 and rs6828477) versus those who were homozygous for the T allele ( $P = 0.46$  and  $P = 0.26$ , respectively; Table 1). When the analysis was restricted to patients who were treated with ranibizumab only ( $n = 432$ ), no significant difference in mean change in VA was detected for patients homozygous for the C allele for rs4576072 ( $P = 0.63$ ) compared

Table 1. Visual Acuity Change from Baseline at 1 Year among Genotype Groups of VEGFR2 Single Nucleotide Polymorphisms rs4576072 and rs6828477 in Comparison of Age-Related Macular Degeneration Treatments Trials and Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularisation

Single Nucleotide Polymorphism Genotype	Ranibizumab and Bevacizumab Combined			Ranibizumab Only		
	No. (%)	Mean Letter Change in Visual Acuity (Standard Deviation)	P Value for Comparison with TT*	No. (%)	Mean Letter Change in Visual Acuity (Standard Deviation)	P Value for Comparison with TT*
		Comparison of Age-Related Macular Degeneration Treatments Trials (n = 835)			Comparison of Age-Related Macular Degeneration Treatments Trials (n = 432)	
rs4576072		P = 0.77 (linear trend)			P = 0.66 (linear trend)	
TT	595 (71)	8.2 (14.5)		312 (72)	8.7 (12.8)	
CT	219 (26)	8.3 (13.6)	0.90	111 (26)	9.9 (12.5)	0.41
CC	21 (3)	5.9 (11.3)	0.46	9 (2)	6.7 (13.0)	0.63
CT or CC	240 (29)	8.1 (13.4)	0.94	120 (28)	9.6 (12.6)	0.50
rs6828477		P = 0.20 (linear trend)			P = 0.01 (linear trend)	
TT	250 (30)	9.2 (13.7)		132 (31)	10.6 (11.2)	
CT	454 (54)	7.8 (14.2)	0.20	230 (53)	9.1 (12.6)	0.29
CC	131 (16)	7.5 (14.8)	0.26	70 (16)	5.5 (15.0)	0.007
CT or CC	585 (70)	7.7 (14.4)	0.16	300 (69)	8.3 (13.3)	0.09
	Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularisation (n = 512) <sup>†</sup>			Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularisation (n = 271)		
rs4576072		P = 0.53 (linear trend)			P = 0.56 (linear trend)	
TT	364 (71)	6.0 (11.9)		196 (72)	6.4 (11.9)	
CT	124 (24)	4.2 (11.4)	0.19	60 (22)	5.6 (12.3)	0.67
CC	20 (4)	7.4 (18.8)	0.62	12 (4)	11.5 (17.4)	0.19
CT or CC	144 (28)	4.7 (12.5)	0.30	72 (27)	6.5 (13.0)	0.93
rs6828477		P = 0.97 (linear trend)			P = 0.13 (linear trend)	
TT	185 (36)	5.0 (12.0)		95 (35)	5.1 (12.8)	
CT	221 (43)	6.6 (11.8)	0.22	121 (45)	6.6 (11.2)	0.39
CC	105 (21)	4.7 (12.8)	0.81	55 (20)	8.3 (13.2)	0.14
CT or CC	326 (64)	5.9 (12.1)	0.43	176 (65)	7.2 (11.8)	0.21

\*Analysis of variance.

<sup>†</sup>Invalid genotype data occurred in 4 patients for rs4576072 and 1 patient for rs6828477 and were excluded from the statistical analysis.

with those homozygous for the T allele. However, for rs6828477, there was a significant difference in mean change in VA for patients homozygous for the T allele (10.6 letters for TT vs. 5.5 letters for CC;  $P = 0.007$ ; Table 1). This difference was in the opposite direction of that reported by Hermann et al.<sup>7</sup>

When we analyzed the possibility of an additive effect on mean change in VA from the number of minor alleles present (0–4 alleles) from the 2 SNPs, we found no association ( $P = 0.24$ , linear trend; Table 2). Similarly, no correlation was observed between mean change in VA and the number of minor alleles present when evaluating patients treated solely with ranibizumab ( $P = 0.07$ , linear trend; Table 2). When analyzing all possible combinations of alleles between the 2 SNPs, there was no significant association noted between the combinations and the mean change in VA ( $P = 0.64$ ; Table 3). Similarly, no correlation was observed when the combination of allele analysis was restricted to patients treated with ranibizumab only ( $P = 0.21$ ; Table 3).

Among IVAN participants, there was no significant difference in mean change in VA between patients homozygous for the C allele (minor allele) for either of the 2 VEGFR2 SNPs versus those who were homozygous for the T allele ( $P = 0.62$  and  $P = 0.81$ , respectively; Table 1). In addition, when the analysis was restricted to patients who were treated with ranibizumab only (n = 271), no

significant difference was detected for patients homozygous for the C allele for either of the 2 VEGFR2 SNPs versus those who were homozygous for the T allele ( $P = 0.19$  and  $P = 0.14$ , respectively; Table 1).

We found no association among IVAN participants between the number of minor alleles present (0–4 alleles) from the 2 SNPs ( $P = 0.72$ , linear trend; Table 2). Furthermore, no correlation was observed between mean change in VA and the number of minor alleles present when evaluating patients treated solely with ranibizumab ( $P = 0.13$ , linear trend; Table 2). When analyzing all possible combinations of alleles between the 2 SNPs, there was no significant association noted between the combinations and the mean change in VA ( $P = 0.73$ ; Table 3). Similarly, no correlation was observed when the combination of allele analysis was restricted to patients treated with ranibizumab only ( $P = 0.87$ ; Table 3).

When the data from both the CATT and IVAN cohorts were combined for the analyses, there was no significant difference in mean change in VA between patients homozygous for the C allele (minor allele) versus those homozygous for the T allele for rs4576072 ( $P = 0.81$ ) or for rs6828477 ( $P = 0.29$ ; data not shown). When the analysis was restricted to patients who were treated with ranibizumab only, no significant difference was detected for patients homozygous for the C allele versus those

Table 2. Visual Acuity Change from Baseline at 1 Year by the Number of Minor Alleles in VEGFR2 Single Nucleotide Polymorphisms rs4576072 and rs6828477 in Comparison of Age-Related Macular Degeneration Treatments Trials and Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularisation

No. of Minor (C) Alleles	Ranibizumab and Bevacizumab Combined		Ranibizumab Only	
	No. (%)	Mean Letters (Standard Deviation)	No. (%)	Mean Letters (Standard Deviation)
Comparison of Age-Related Macular Degeneration Treatments Trials				
0	183 (22)	9.3 (14.2)	97 (22)	10.9 (10.9)
1	387 (46)	8.0 (14.2)	193 (45)	8.7 (12.8)
2	207 (25)	7.9 (14.2)	120 (28)	8.5 (13.4)
3	56 (7)	7.2 (14.2)	22 (5)	5.6 (15.2)
4	2 (0)	0.0 (0.0)	0 (0)	—*
P value (linear trend)		0.24		0.07
Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularization				
0	133 (26)	5.3 (11.2)	69 (26)	5.0 (10.9)
1	196 (39)	6.3 (12.6)	106 (40)	6.2 (12.5)
2	145 (29)	5.3 (12.1)	75 (28)	7.8 (13.6)
3	26 (5)	3.7 (10.8)	15 (6)	5.1 (4.4)
4	7 (1)	5.7 (22.5)	3 (1)	19.7 (17.8)
P value (linear trend)		0.72		0.13

\*No study participants had 4 minor alleles in the ranibizumab-only group.

homozygous for the T allele for rs4576072 ( $P = 0.51$ ) or for rs6828477 ( $P = 0.25$ ; data not shown).

Finally, for both CATT and IVAN, no statistically significant association was observed between mean change in VA and either of the 2 VEGFR2 SNPs tested when the data from 3 months were analyzed (data not shown).

## Discussion

We evaluated the association of 2 VEGFR2 SNPs with response to anti-VEGF therapy in 2 independent, large patient cohorts because a strong association with VA had been

reported previously by Hermann et al.<sup>7</sup> We found no statistically significant associations that would support the findings of the Hermann et al study in our analysis that involved a total of 1347 patients with neovascular AMD. In their study of 366 patients evaluating the pharmacogenetic effects of 126 SNPs from 9 genes, only 2 SNPs (rs4576072 and rs6828477) were found to be associated with greater VA improvement in patients treated with ranibizumab. However, most of their analyses did not account for their evaluation of many ( $n = 126$ ) different SNPs. Although there was a statistically significant association ( $P < 0.025$ ) within the CATT data for rs6828477 in patients treated with

Table 3. Visual Acuity Change from Baseline at 1 Year by the Combination of VEGFR2 Single Nucleotide Polymorphisms rs4576072 and rs6828477 in Comparison of Age-Related Macular Degeneration Treatments Trials and Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularisation

Single Nucleotide Polymorphism Genotype	Ranibizumab and Bevacizumab Combined			Ranibizumab Only		
	rs4576072			rs4576072		
	TT	CT	CC	TT	CT	CC
Mean (SD) in CATT						
rs6828477						
TT	9.3 (14.2)	9.1 (12.6)	—	10.9 (10.9)	9.5 (12.2)	—
CT	7.8 (14.5)	8.1 (13.8)	5.8 (12.0)	8.5 (12.9)	11.1 (11.6)	5.3 (13.4)
CC	7.5 (14.9)	7.7 (15.0)	—	5.4 (14.8)	5.7 (16.5)	—
		$P = 0.64$			$P = 0.21$	
Mean (SD) in IVAN						
rs6828477						
TT	5.3 (11.2)	3.7 (13.2)	10.4 (22.4)	5.0 (10.9)	4.8 (15.8)	—
CT	7.0 (12.3)	5.2 (10.6)	6.9 (14.4)	6.6 (11.6)	6.6 (11.4)	6.5 (5.2)
CC	5.1 (12.5)	2.3 (9.0)	5.7 (22.5)	8.3 (13.9)	4.4 (4.1)	—
		$P = 0.73$			$P = 0.87$	

CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; IVAN = Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with Age-Related Choroidal Neovascularisation; SD = standard deviation; — = mean (SD) was not calculated because the number of patients was fewer than 5.



ranibizumab, the allele associated with lower visual acuity in the study by Hermann et al was associated with better visual acuity in the CATT patients, and no association was identified among the IVAN patients or the combined group of patients treated with ranibizumab or bevacizumab in each study. In addition to the possibility that the associations were attributable to chance variation, it is possible that the Hermann et al cohort was different given that there were no baseline variables that were associated with 1-year visual outcomes in that study. In CATT and most other neovascular AMD studies, age and baseline visual acuity, for example, were associated strongly with 1-year visual outcomes.<sup>9–12</sup>

The rationale as to why these 2 SNPs located in the *VEGFR2* gene influence the visual outcome of anti-VEGF treatment is not clear. Hermann et al<sup>7</sup> suggest that these SNPs lead to altered expression of *VEGFR2*, leading to a benefit on visual acuity of VEGF neutralization by ranibizumab. However, both rs4576072 and rs6828477 are located in the intronic sequences, and to our knowledge, there are no reports that have tested this hypothesis and confirmed that either of these polymorphisms influence the expression or functional activity of *VEGFR2*.

In conclusion, the combined analysis of data from the CATT and IVAN trial does not support a pharmacogenetic association between the 2 *VEGFR2* SNPs, rs4576072 and rs6828477, and the visual acuity response to anti-VEGF therapy in patients with neovascular AMD.

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## Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

**AMD** = age-related macular degeneration; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **IVAN** = Alternative Treatments to Inhibit Vascular Endothelial Growth Factor in Patients with

Age-Related Choroidal Neovascularisation; **SNP** = single nucleotide polymorphism; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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## Pictures & Perspectives

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### Central Retinal Artery Occlusion in a 21-Year-Old Boxer

A 21-year-old man with a left central retinal artery occlusion with an embolus in the inferior arcade (*arrow*) that occurred following carotid artery dissection after being punched in the neck while boxing. A cilioretinal artery preserved a small central island of light perception vision.

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