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Predictors of Response to Intravitreal Anti-Vascular Endothelial Growth Factor Treatment of Age-Related Macular Degeneration

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Abstract

- **PURPOSE:** To identify factors that influence visual and anatomic response to treatment with intravitreal anti-vascular endothelial growth factor (VEGF) for neovascular age-related macular degeneration (AMD).
- **DESIGN:** Observational cohort study.
- **METHODS:** Seventy-two patients were included in this study. Best corrected Snellen visual acuity (VA) and central foveal thickness measured on optical coherence tomography (OCT) at time of treatment and post-treatment follow-up visits were recorded. Associations between demographic, behavioral, and genetic risk factors and the two outcomes were analyzed using mixed effects linear regression models. Two loci in complement factor H (*CFH*) were included in a risk score to determine the association between *CFH* risk and improvement in VA and central foveal thickness.
- **RESULTS:** There was a minimal but not statistically significant improvement in VA in the overall study population following anti-VEGF treatment (mean: 3.7 ± 3.0 letters). Significant improvement in VA was observed for the non-risk *CFH* Y402H genotype ($P < 0.001$) and for a low *CFH* risk score ($P = 0.019$). Regarding the outcome of change in central foveal thickness, improvement was noted in all genotype groups, but reduction after treatment was significantly higher in the low *CFH* risk score group ($P = 0.033$). A significant improvement in mean VA was observed for smokers ($P < 0.001$), but this relationship was not observed for central foveal thickness.
- **CONCLUSION:** After anti-VEGF therapy, significant improvement in VA was observed for low risk *CFH* genotypes and subjects with a low risk score. There was a statistically significant

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reduction in central foveal thickness overall, and subjects with a low *CFH* risk score improved more than the high risk group.

Prior to the advent of anti-vascular endothelial growth factor (VEGF) treatment, neovascular age-related macular degeneration (AMD) was a leading cause of irreversible vision loss in people over age 50 in the Western World.¹ Pivotal trials such as the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and Anti-vascular endothelial growth factor Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (ANCHOR) confirmed the efficacy of ranibizumab^{2,3} and subsequent studies, such as the Comparison of AMD Treatments Trial (CATT), demonstrated that the use of bevacizumab yielded similar visual acuity (VA) and anatomic outcomes when comparing identical treatment regimens.⁴ Despite the overall success of anti-VEGF medications, in clinical practice there are variations in response to these drugs among individuals. Differences in relative improvement in vision, decrease in intraretinal and subretinal fluid, and length of effect of the drug in each patient have led to a variety of proposed treatment regimens, aiming to minimize treatment burden and cost while still maintaining maximum potential benefits.

Several reports have identified genetic as well as modifiable risk factors, including body mass index (BMI) and smoking history, as contributors to increased susceptibility to development and progression to neovascular AMD.^{5,6} There are numerous confirmed genetic variants implicated in the development of neovascular AMD.⁶ It has been proposed that these same genetic and behavioral risk factors may contribute to varying responses to treatment with anti-VEGF. This hypothesis that underlying genetic susceptibility can modify treatment responsiveness has gained considerable attention with recent reports suggesting that the effects of antioxidant and zinc supplements on rate of progression of AMD vary according to genotype,⁷ although reports are inconsistent.^{8,9} Many studies have also been conducted to assess associations between some of these factors and response to treatment after anti-VEGF agents. Despite the growing body of literature on this subject, results are conflicting and it is difficult to contrast studies. Methods and outcome measures differ, and there is no uniform consensus on the definition of good and poor response. There are a limited number of studies on the effect of behavioral or demographic factors on response to treatment, and these also have conflicting results.

At the time of this study, we reviewed existing literature on genetic and behavioral influences that affect response to treatment with intravitreal anti-VEGF medication for neovascular AMD, and we employed methods of analysis which may be used for future studies with similar aims. Unlike some previously published reports, we analyzed behavioral and demographic characteristics as well as several recently reported genetic loci. The impact of the various factors individually as well as the combined effect of potentially predictive genetic and behavioral characteristics on response to anti-VEGF therapy were assessed.
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SUBJECTS AND METHODS

• SUBJECTS:

A retrospective chart review was conducted for 220 patients from a single institution (New England Eye Center, Boston, MA) who had been concurrently or previously enrolled in genetic and epidemiologic studies of the etiology of AMD, and who were diagnosed with neovascular AMD. This research adhered to the tenets of the Declaration of Helsinki and was performed under appropriate institutional review board protocol from the New England Eye Center and Ophthalmic Epidemiology and Genetics Service at Tufts Medical Center. Signed informed consent was obtained from all subjects.

Seventy-two subjects with subretinal or intraretinal fluid on optical coherence tomography (OCT) at the time of first injection were included in this analysis. The remaining patients were excluded as follows: 1) another treatment for neovascular AMD was given within three months prior to the first injection with bevacizumab or ranibizumab (N=17); 2) there was no history of treatment with bevacizumab or ranibizumab (N=24); 3) injections were given at another institution during the first 12 months of treatment (N=31); 4) no intra-retinal or subretinal fluid was seen on optical coherence tomography (OCT) at the time of first injection (N=13); or 5) a subject had incomplete data at the time of any treatment or follow up visit, or less than 12 months follow up (N=53). Only the first eye treated with anti-VEGF intravitreal injection was included in the analysis. Best corrected Snellen VA and central foveal thickness as measured by OCT imaging, performed on either the Stratus or Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA), were recorded for each visit in which treatment was received, and each post-treatment follow up visit for a period of one year, as well as at 6 month and 12 month visits. Central foveal thickness measurements were recorded as the central value on the retinal thickness map, calculated by standard OCT retinal mapping software. Diagnosis of neovascular AMD was made by a retina specialist on the basis of a dilated fundus examination, OCT findings, color fundus photography, and fluorescein angiography. Initial and subsequent anti-VEGF treatments were given at the discretion of the treating physician, and were based on VA, a dilated fundus examination, and OCT results during follow-up visits. Demographic (age, sex, and education) and behavioral (BMI and smoking history) data were also evaluated. Genotypes were derived from genotyping and sequencing platforms as previously described.^{12,13} The following AMD-related genes were assessed as risk factors in these analyses: *CFH*, *CFB*, *C3*, *CFI*, *VEGFA*, *TGFBR1*, *LIPC*, *ABCA1*, *CETP*, *APOC1/APOE*, *TNFRSF10A*, *SLC16A8*, *COL8A1*, *COL10A1*, *ARMS2/HTRA1*, *RAD51B*, *DDR1*, *ADAMTS9/ADAMTS9-AS2*, and *HSPH1/B3GALT1*⁶

• LITERATURE REVIEW:

A PubMed search using the terms “age related macular degeneration genetic response to treatment” was conducted at the time of the study. English language research articles assessing the association between genetic variables and response to intravitreal anti-VEGF treatment that were available before October 16, 2014 were included in the review. A Google Scholar search was also conducted using the same terms and inclusion criteria. Review or meta-analysis articles, as well as those that did not evaluate genetic risk factors, were not included. Details of these studies are included in Supplemental Table 1.

• STATISTICAL ANALYSIS:

VA measurements at baseline, 6 months, and 12 months were assessed. OCT central foveal thickness measurements were analyzed at baseline and either 6 or 12 months follow up. Snellen VA was transformed to logarithm of the minimum angle of resolution (LogMAR) units by the following calculation: $\log(\text{VA})/20$. Means and standard deviations of $\log(\text{VA})/20$ and OCT central foveal thickness were calculated for each time point. Higher mean values of $\log(\text{VA})/20$ were indicative of worse VA. Mean change and standard error using Early Treatment Diabetic Retinopathy Study (ETDRS) acuity in letters were also calculated.

Longitudinal analyses were conducted to examine the association between demographic, behavioral, and genetic factors and change in VA and central foveal thickness measurements after anti-VEGF treatments. The associations between risk factors and the two outcomes over time were analyzed using mixed effects linear regression models. Improvement in these outcomes was assessed based on slope, or change over time. A negative slope indicates improvement over time, a positive slope indicates worsening, and a slope of zero is equal to no change. Statistical significance was assessed using standard P values and P values for heterogeneity (P_{het}). P values were obtained to assess whether the change for each level of a variable was significantly different from zero (i.e. no change) for both VA and central foveal thickness. P_{het} assessed whether the change over time for distinct levels within one particular risk factor significantly differed from each other for a particular outcome.

Changes in VA and central foveal thickness over time were also evaluated according to risk score category. These analyses utilized an externally derived and previously calculated composite score used to assess risk of progression to advanced AMD.^{10,11} The risk score was calculated using regression coefficients of all demographic, environmental, genetic, and ocular factors. The hazard ratio for the i th subject is given from the Cox proportional hazards model by $\lambda_i = \exp(\sum_{j=1}^J \beta_j x_{ij})$, where β_j is the regression coefficient for the j th variable and x_{ij} is the value of the i th variable for the i th subject. The variables included in the score are as follows: 10 genetic loci, age, sex, education, BMI, and smoking status. The low risk category was defined as less than the median score, and the high risk category was defined as greater than or equal to the median risk score.

A risk score for complement factor H (CFH) was calculated using the number of risk alleles for selected single nucleotide polymorphisms (SNPs). The score was comprised of rs1061170 and rs1410996, with subjects having 0 to 4 risk alleles for these selected CFH variants. Groups for each score were classified as low risk (0 to 2 risk alleles) or high risk (3 to 4 risk alleles).

We also calculated similar risk scores for complement factor I (CFI), as variants in CFI have been implicated as potentially related to outcome after Lampalizumab treatment in a small study (Regillo CD. Lampalizumab (anti-factor D) in patients with geography atrophy: the MAHALO phase 2 results. Paper presented at: *the 2013 Annual Meeting of the American Academy of Ophthalmology*; November 16-19, 2013; New Orleans, LA.). The CFI risk score was comprised by the number of risk alleles for CFI rare variants (0 to 2). The

common *CFI* variant, rs10033900, was also evaluated based on number of risk alleles (0 to 2). *CFI* risk was classified as low or high risk by the number of risk alleles present (0 and 1 to 2, respectively).

As this study is considered exploratory, multiple comparisons and interactions between risk factors were not assessed. All analyses were conducted using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA). The alpha level for statistical significance was set a priori at $P < 0.05$.

RESULTS

Table 1 shows VA measurements at baseline, 6 months, and 12 months for selected demographic, behavioral, and genetic risk factors. The overall mean change in VA from baseline to 12 months was -0.2 LogMAR units, which is an improvement of 3.65 letters over one year. This change, however, was not statistically significant. A greater improvement in mean VA over time was observed in the 55 to 70 year old age group, among males, and among ever smokers (current and past smokers). Improvement was also exhibited by subjects carrying the non-risk genotype (TT) for *CFHY402H*. Specifically, subjects with the TT genotype improved by 22.0 ± 6.6 letters, whereas there was no significant change in the other two genotype groups. Similar results were obtained for *CFH*rs1410996. No significant trend relating improvement in VA to the number of risk alleles for other AMD SNPs was apparent (*CFB*, *C3*, *CFI*, *VEGFA*, *TGFBR1*, *ABCA1*, *CETP*, *APOC1/APOE*, *TNFRSF10A*, *COL8A1*, *COL10A1*, *ARMS2/HTRA1*, *RAD51B*, *DDR1*, *ADAMTS9/ADAMTS9-AS2*, *HSPH1/B3GALT1*). Some differences in response were noted for *LIPC* and *SLC16A8*, but these differences were not statistically significant.

The association between central foveal thickness at baseline and final measurements for the variables listed above is presented in Table 2. There was a statistically significant reduction in central foveal thickness in the overall study population of $94 \mu\text{m}$ ($P < 0.0001$). All categories for each risk factor also had a reduction in mean central foveal thickness over time.

Longitudinal analyses of the change in VA after anti-VEGF treatment are presented in Table 3 for selected demographic and behavioral factors, as well as for five loci in the complement pathway genes. The complement genes were specifically illustrated due to the higher levels of improvement suggested for non-risk genotype carriers (Table 1). Subjects who were homozygous for the non-risk (T) allele for *CFHY402H* demonstrated significantly greater improvement over time than did subjects who were either heterozygous or homozygous for the risk (C) allele ($P_{\text{trend}} = 0.026$). None of the other complement pathway genes were significantly associated with improvement in VA over time. Younger individuals and males tended to have better visual outcomes, but differences were not significant. Individuals who had ever smoked had greater visual improvement ($P = 0.0003$). Non-smokers had a mild worsening of VA, although these results were not statistically significant ($P = 0.058$). There were no significant differences in outcomes between bevacizumab and ranibizumab, the two types of anti-VEGF treatments.

Table 4 displays the association between change in central foveal thickness after anti-VEGF treatment and each risk factor described above. All categories for each demographic, behavioral, and genetic factor were significantly associated with reduction in central foveal thickness, comparing final to baseline values (all P values < 0.05). However, the change in central foveal thickness over time did not differ among specific categories for each risk factor considered. Each genotype group for the five SNPs evaluated demonstrated a statistically significant improvement in central foveal thickness (all $P < 0.05$), although the observed improvement did not significantly differ among genotypes for each SNP (all $P_{\text{het}} > 0.05$).

Supplemental Tables 2 and 3 present the association between the 15 additional AMD SNPs evaluated and change in VA and central foveal thickness after anti-VEGF treatment, respectively. Subjects who were homozygous for the protective allele (T) of *LIPC* exhibited a worsening in VA ($P = 0.02$); however, there were only four subjects in this group. Subjects with at least one non-protective allele (C) in *LIPC* demonstrated a significant improvement in central foveal thickness as measured by OCT ($P < 0.0001$). None of the other genes evaluated showed differential responses to anti-VEGF treatment.

The relationships between the *CFH* risk score and change in VA and central foveal thickness are shown in Table 5 and Figures 1 and 2. There was a significant improvement in VA for a low *CFH* risk score with no change present in the high risk group. For OCT central foveal thickness, subjects in the low *CFH* risk score group exhibited significantly higher levels of improvement over time, although both high and low risk score groups improved. For VA, $P_{\text{het}} = 0.019$, and for central foveal thickness, $P_{\text{het}} = 0.033$. In an additional analysis of VA, the effect of the *CFH* risk score was only present in ever smokers. Improvement in VA over time as measured by LogMAR among ever smokers was -0.54 ± 0.12 in the low *CFH* risk score group, and -0.10 ± 0.08 in the high risk group ($P_{\text{interaction}} < 0.002$). Among never smokers, the decline in VA over time was 0.15 ± 0.20 in the low risk group versus 0.23 ± 0.14 in the high risk group ($P_{\text{interaction}} > 0.72$). Although there was a larger improvement in VA in past or current smokers compared to never smokers, this finding is preliminary and requires additional confirmation through future studies.

The relationships between *CFI* risk alleles and change in VA and OCT central foveal thickness were also examined for the common and rare *CFI* variants. Change in VA over time was not significantly associated with *CFI* risk alleles. Although both high and low risk score groups exhibited a significant improvement in central foveal thickness, the difference in improvement between the low and high risk groups was not statistically significant.

A score combining demographic, behavioral, and genetic variables was also assessed. The median composite risk score for this cohort of subjects with neovascular AMD was 1.93. The estimated change in LogMAR VA per year was -0.15 for the low risk score category (score < 1.93) and -0.01 for the high risk category (score ≥ 1.93), suggesting that the low risk group had more improvement in VA (data not shown). This result shows a trend similar to results observed for the *CFH* risk score presented in Table 5, although these analyses of the composite risk score were not statistically significant ($P = 0.32$). The outcome based on

central foveal thickness did not vary according to the low and high composite risk score groups.

DISCUSSION

Significant improvement in VA was observed for low risk *CFH* genotypes and among subjects with a low *CFH* risk score. In our overall study population, there was a statistically significant reduction in central foveal thickness. All genotypes showed a reduction in central foveal thickness, but individuals with a low *CFH* risk score had a greater improvement in this outcome after treatment compared to those in the high risk group.

Among the non-genetic variables evaluated, improvement in mean VA over time was seen in the 55 to 70 year old age group, among males, and among smokers. However, only a history of smoking demonstrated a significant difference in improvement in VA over time compared to non-smokers. For the outcome based on central foveal thickness, favorable response was observed for all non-genetic variables, although the categories within each risk factor did not significantly differ from each other (e.g, low, medium, and high BMI) in reduction of central foveal thickness.

Studies in several different ethnic populations seem to corroborate our results, suggesting that perhaps there is an association between *CFH* genotype and response to treatment with respect to VA.^{15–20} One of these studies reported that high risk alleles in the *CFH* gene are associated with a worse response to anti-VEGF treatment than low risk alleles, whether that response is measured by VA or anatomical resolution as noted on OCT.²⁰ However, the CATT and Inhibition of VEGF in Age-related Choroidal Neovascularisation (IVAN) trials reported no association between individual genotypes (*CFH*, *ARMS2/HTRA1*, *C3*, *VEGF*, and *VEGFR2*) and response to treatment.^{21,22} In the CATT trial, however, there were significant differential effects of treatment for change in foveal thickness according to *CFH* Y402H genotype ($P_{\text{trend}} = 0.03$).²¹ These results are in the same direction as in Table 5: subjects who were homozygous for the nonrisk allele for *CFH* Y402H demonstrated greater improvement in VA over time compared to those with high risk genotypes. When both *CFH* genotypes were included in a combined *CFH* risk score, the relationship between high risk score and worse VA remained significant. The potential value of evaluating a genetic risk score is emphasized by the finding that reduction in central foveal thickness differed according to a *CFH* risk score combining two loci, but not when each SNP was evaluated separately. Another study showed that a greater number of high risk alleles in *CFH* and *ARMS2* were associated with less visual improvement after anti-VEGF treatment.²³ It is possible that there are interactions between VEGF inhibition, genetic susceptibility, and complement activation that may lead to varying response patterns among individuals with different *CFH* genotypes.

While this study was limited by its retrospective design, small sample size, and univariate analyses of the VA and OCT outcomes, results suggest that assessment of risk scores for genes with similar function might yield more consistent results across studies. Another result of note is that there was no significant association between a previously derived composite risk score for development of advanced AMD and response to treatment with intravitreal

anti-VEGF treatment in this cohort. This may be due to the sample size, but could also be related to the fact that the composite risk score takes into account several behavioral and genetic factors in addition to those that could have the greatest impact on response to treatment. Factors that increase risk for developing neovascular AMD may not be the same as those influencing response to treatment, implying that the same risk score used to predict development of advanced disease may not be as strong a predictor for outcomes after treatment.

Findings from the Lampalizumab Phase IB/II trial (MAHALO study, presented at American Academy of Ophthalmology meeting, November 2013), a Phase II clinical trial investigating lampalizumab for treatment of geographic atrophy due to dry AMD, suggested that a *CFI* polymorphism was associated with different levels of response to lampalizumab. Patients treated monthly with lampalizumab who did not have the common *CFI* variant had a 20% reduction in the rate of progression of geographic atrophy (measured by area of geographic atrophy assessed by autofluorescence), whereas those who did have this *CFI* variant had a 44% reduction in progression. Given these findings, we analyzed the number of risk alleles for *CFI* variants and their effect on VA and central foveal thickness. No statistically significant differences between low versus high number of risk alleles were noted when considering both common and rare variants in this gene.

Thus far, the literature is not conclusive regarding the effect of demographic and behavioral factors on response to treatment. Although not statistically significant, the small sample of nonsmokers included in our cohort did not have an improvement in VA. This result was unexpected given the high risk of disease progression noted in smokers. Whereas one study found that increasing number of pack-years of smoking was associated with decreased VA (Menger JF, et al. *IOVS*. 2012;53(2): E-abstract 857), another study corroborated our results, showing that a history of smoking was associated with a positive visual outcome (Inglehearn CF, et al. *IOVS*. 2012;53(7): E-abstract 3325). One possible explanation, other than this being a chance finding, is that AMD in patients with a smoking history may represent a more “typical” form of the disease, thereby responding more favorably to standard treatment, whereas those who develop neovascular AMD without a history of ever smoking may have different behavioral and genetic risk profiles, and thus not respond as well to anti-VEGF medication. Further investigation is necessary, and these findings do not suggest that patients with AMD should start or continue to smoke.

It is difficult to compare the results of one pharmacogenetic study with another due to differences in study design, such as inclusion and exclusion criteria as well as study length. The lack of a universal definition of “good” and “poor” response used throughout the current literature also complicates one’s ability to draw conclusions from the cumulative data (Supplemental Table 1). Change in central foveal thickness is often included as an outcome measure, but it is unclear how much change should be indicative of an adequate response to a therapy. VA is the most commonly used outcome measure, but the amount of change defined as “improvement”, or lack thereof, varies greatly among all of the reports. There is also a “ceiling” effect when using VA to measure response to treatment. That is, patients with relatively good initial VA have less room for improvement, and may thus skew results towards the appearance of “poor” response due to a smaller relative change in vision. In

addition, VA tends to fluctuate in AMD patients, and often they report marked subjective changes despite minimal improvement in measured visual acuity.

VA is an established surrogate marker for visual function. However, near-normal VA measurements may not reflect changes in other visual function parameters such as glare-sensitivity, contrast sensitivity, reading speed and visual field.²⁴ Sunness and colleagues showed that patients with paracentral geographic atrophy due to dry AMD had significant decreases in contrast sensitivity and other markers of visual function despite maintaining good VA.²⁵ Other tests of visual function, such as microperimetry, have also been shown to be more sensitive markers of outer retinal integrity and retinal sensitivity in neovascular AMD.^{26,27} While it is beyond the scope of this paper to suggest alternative definitions of “good” and “poor” response to treatment, these other markers may provide a more sensitive measure of clinically relevant changes, and may thus be useful outcome measures in future studies evaluating the progression of disease and effects of treatment.

In conclusion, this study showed an independent, statistically significant association between better VA after anti-VEGF treatment and low risk *CFH* genotypes and a history of smoking. A greater reduction in central foveal thickness was also noted with a lower *CFH* risk score. Our results add to the growing literature on this subject, and highlight the need for continued research on factors that may influence response to treatment in neovascular AMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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All authors attest that they meet the current ICMJE requirements to qualify as authors.

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FIGURE 1. Change in visual acuity (VA) over time for low versus high complement factor *H* (*CFH*) risk scores after intravitreal anti-vascular endothelial growth factor treatment for age-related macular degeneration.

Among subjects with a low *CFH* risk score, there was a notable improvement in VA over time (6.33 ± 2.40 letters) compared to no demonstrable improvement for subjects in the high risk group ($P_{\text{het}} = 0.019$). VA is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) acuity in letters. Standard error is illustrated by vertical error bars.

FIGURE 2. Change in central foveal thickness as measured by optical coherence tomography (OCT) for low versus high complement factor *H* (*CFH*) risk scores after intravitreal anti-vascular endothelial growth factor treatment for age-related macular degeneration.

Among subjects with a low *CFH* risk score, there was greater reduction in central foveal thickness over time compared to the high risk group ($P_{\text{het}} = 0.033$). Standard error is illustrated by vertical error bars.

Table 1.

Response to Intravitreal Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration and Change in Visual Acuity Over Time for Selected Demographic, Behavioral, and Genetic Characteristics

	VA (LogMAR) ^a at Baseline			Change in VA from Baseline to 6 Months		Change in VA from Baseline to 12 Months		Change in ETDRS ^b VA from baseline to 12 months	
Variable	N ^c	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Error
Overall	68	1.7	1.0	-0.2	0.9	-0.2	1.1	3.7	3.0
Age									
55-70	23	1.6	1.0	-0.5	0.7	-0.7	0.8	14.4	3.5
71-78	23	1.7	1.1	0.1	1.0	0.3	1.4	-5.7	6.2
79-90	22	1.9	1.0	-0.05	0.8	-0.1	1.0	2.1	4.5
Sex									
Male	24	1.9	1.1	-0.4	0.7	-0.5	1.2	11.5	5.4
Female	44	1.6	10.2	-0.04	1.0	0.03	1.0	-0.7	3.3
Education									
High School	22	1.7	1.1	0.002	0.8	0.2	1.2	-3.4	5.4
> High School	46	1.7	1.0	-0.2	0.9	-0.3	1.1	7.2	3.4
Body Mass Index									
< 25	24	1.9	1.2	-0.3	0.9	-0.2	1.2	5.0	5.4
25-29.9	26	1.6	1.0	0.1	0.8	-0.1	1.1	1.2	4.5
30+	18	1.7	0.9	-0.4	0.9	-0.2	1.1	5.4	5.8
Smoking									
Never smoker	26	1.5	0.8	0.1	1.0	0.4	1.2	-8.4	5.1
Ever smoker	42	1.9	1.2	-0.3	0.7	-0.5	0.9	11.1	3.1
Medication									
Bevacizumab	18	1.5	1.2	-0.3	1.2	-0.3	1.1	7.6	5.8
Ranibizumab	50	1.8	1.0	-0.1	0.8	-0.1	1.1	2.2	3.5
Genetic Variables^d									
Complement Genes									
CFH: rs1061170 (Y402H)									
TT	14	2.2	1.3	-0.6	0.9	-1.0	1.1	22.0	6.6
CT	34	1.7	1.0	0.04	0.9	0.1	1.1	-2.4	4.0
CC	20	1.4	0.8	-0.2	0.9	-0.04	0.9	1.0	4.5
CFH: rs1410996									
TT	3	1.3	1.0	-0.4	0.7	-0.7	1.4	16.0	17.2
CT	15	1.7	1.2	0.006	0.9	-0.3	1.3	5.6	7.1
CC	50	1.8	1.0	-0.2	0.9	-0.1	1.1	2.3	3.3
CFB: rs541862									
TT	61	1.8	1.1	-0.1	1.0	-0.4	1.2	3.2	3.1
CT	7	1.6	0.8	-0.2	0.9	-0.1	1.1	7.7	9.9
C3: rs2230199 (R102G)									

	VA (LogMAR) ^a at Baseline			Change in VA from Baseline to 6 Months		Change in VA from Baseline to 12 Months		Change in ETDRS ^b VA from baseline to 12 months	
Variable	N ^c	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Error
CC	43	1.7	1.0	-0.1	1.0	-0.2	1.2	3.9	3.9
CG	22	1.9	1.2	-0.3	0.5	-0.2	1.1	4.6	5.1
GG	3	1.6	1.4	0.6	1.3	0.3	0.6	-7.3	7.3
CFI: rs10033900									
CC	20	1.6	1.0	-0.2	0.9	-0.3	1.0	6.7	4.9
CT	33	1.7	1.1	-0.2	1.0	-0.1	1.1	3.0	4.0
TT	15	1.9	1.0	-0.1	0.8	-0.04	1.4	1.0	8.0
Angiogenesis									
VEGFA: rs943080									
CC	11	1.2	0.5	0.1	1.1	0.1	1.3	-1.5	8.8
CT	38	1.8	1.1	-0.3	0.6	-0.3	1.0	6.1	3.4
TT	19	1.9	1.4	-0.1	1.2	-0.1	1.3	1.8	6.5
TGFBRI: rs334353									
TT	45	1.7	1.1	-0.2	0.9	-0.2	1.0	4.2	3.4
GT	19	1.7	1.0	0.004	0.9	-0.1	1.4	1.6	7.0
GG	4	2.5	1.1	-0.4	0.3	-0.4	0.3	7.8	3.3
Lipid Pathway									
LIPC: rs10468017									
TT	4	1.2	0.5	0.5	1.1	1.3	1.3	-27.5	14.5
CT	28	1.7	0.9	-0.2	0.7	-0.2	0.8	3.6	3.1
CC	36	1.8	1.2	-0.2	1.0	-0.3	1.2	7.1	4.5
ABCA1: rs1883025									
CC	40	1.9	1.0	-0.2	1.0	-0.3	1.1	5.6	3.9
CT	27	1.5	1.1	-0.2	0.8	-0.03	1.1	0.7	4.7
TT	1	1.1	-	0.2	-	-0.2	-	4.0	-
CETP: rs3764261									
CC	31	1.8	1.1	-0.1	0.9	-0.2	1.3	4.4	4.9
AC	27	1.6	1.0	-0.2	0.7	-0.1	0.9	2.2	3.7
AA	10	2.0	1.1	-0.2	1.3	-0.2	1.3	5.4	9.3
APOC1/APOE: rs4420638									
AA	48	1.8	1.0	-0.2	0.9	-0.2	1.1	5.2	3.5
AG/GG	20	1.7	1.1	-0.1	1.0	0.01	1.1	-0.1	5.6
Immune/Inflammatory									
TNFRSF10A: rs13278062									
TT	20	1.5	0.9	-0.1	0.7	0.1	1.1	-2.6	5.3
GT	33	1.8	1.1	-0.1	0.8	-0.2	1.0	4.5	3.9
GG	15	1.9	1.2	-0.4	1.3	-0.5	1.3	10.1	7.3
SLC16A8: rs8135665									
CC	46	1.8	1.1	-0.3	0.8	-0.2	1.0	5.2	3.2
CT	19	1.6	0.9	0.01	1.1	-0.2	1.3	5.1	6.6

	VA (LogMAR) ^a at Baseline			Change in VA from Baseline to 6 Months		Change in VA from Baseline to 12 Months		Change in ETDRS ^b VA from baseline to 12 months	
Variable	N ^c	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Error
TT	3	2.3	0.4	0.7	1.2	1.3	0.9	-28.7	11.7
Extracellular Matrix									
<i>COL8A1</i> : rs13095226									
TT	54	1.8	1.1	-0.2	0.9	-0.2	1.1	4.0	3.3
CT	14	1.3	0.9	-0.1	0.7	-0.1	1.1	2.3	6.6
<i>COL10A1</i> : rs1064583									
AA	32	1.7	1.1	-0.3	1.0	-0.3	1.3	6.6	5.1
AG	24	1.6	0.9	-0.1	0.9	-0.04	1.1	0.9	4.7
GG	12	2.1	1.2	-0.04	0.7	-0.1	0.6	1.3	3.6
Other									
<i>ARMS2/HTRA1</i> : rs10490924 (A69S)									
GG	27	1.7	1.1	-0.1	0.8	-0.2	1.1	4.0	4.7
GT	23	1.9	1.1	0.009	1.1	-0.2	1.4	3.8	6.3
TT	18	1.6	1.1	-0.4	0.5	-0.1	0.7	2.9	3.7
<i>RAD51B</i> : rs8017304									
GG	9	1.6	1.1	-0.2	1.4	-0.3	1.3	6.3	9.6
AG	30	1.8	1.0	-0.2	0.7	-0.2	0.9	3.9	3.7
AA	29	1.7	1.1	-0.2	0.9	-0.1	1.3	2.6	5.1
<i>DDR1</i> : rs3094111									
CC	45	1.7	1.0	-0.04	1.0	-0.2	0.9	3.4	3.0
CT	19	1.8	1.3	-0.4	0.8	-0.4	1.4	8.0	7.0
TT	4	1.7	0.9	-0.3	0.5	0.6	1.6	-14.0	16.8
<i>ADAMTS9/ADAMTS9-AS2</i> : rs6795735									
CC	16	1.5	1.0	-0.3	0.9	-0.3	0.8	7.3	4.1
CT	31	1.7	0.9	-0.03	0.9	0.004	1.2	-0.06	4.7
TT	21	2.0	1.3	-0.3	0.8	-0.3	1.2	6.4	5.9
<i>HSPH1/B3GALT1</i> : rs9542236									
TT	19	2.0	1.0	0.1	0.8	0.1	1.3	-1.5	6.8
CT	37	1.8	1.1	-0.4	0.8	-0.6	0.8	12.1	2.7
CC	12	1.0	0.4	0.21	1.0	0.7	1.3	-14.4	8.3

^aVisual acuity (VA) as measured by the logarithm of the minimum angle of resolution (LogMAR). All VA values are natural log transformed, and are calculated as follows: $\ln(x/20)$. For example, the mean baseline VA for males is 1.9 after transformation, which equals $e^{[1.90 + \ln(20)]}$, or $e^{4.8957}$. Therefore, the mean VA = 20/134. Higher mean values indicate worse VA.

^bEarly Treatment Diabetic Retinopathy Study (ETDRS) values for VA represents mean change in number of letters from baseline to 12 months, calculated as the mean number of letters at 12 months minus the mean number of letters at baseline.

^cAll subjects (n=68) have complete data at baseline, 6 month, and 12 month VA measurements.

^dGenetic variables are presented in the following order: homozygous for non-risk allele, heterozygous for risk allele, and homozygous for risk allele. The exceptions to this convention are *CFB*: rs541862 and *COL8A1*: rs13095226, presented as homozygous for non-risk allele and heterozygous for risk allele (no subjects were homozygous for risk allele), and *LIPC*: rs10468017 and *RAD51B*: rs8017304, presented as homozygous for protective allele, heterozygous for protective allele, and homozygous for non-protective allele.

Table 2.

Response to Intravitreal Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration and Change in Central Foveal Thickness as Measured By Optical Coherence Tomography Over Time for Selected Demographic, Behavioral, and Genetic Characteristics

	OCT ^a Central Foveal Thickness at Baseline			Change in OCT Central Foveal Thickness from Baseline to Final	
Variable	N ^b	Mean	Standard Deviation	Mean	Standard Deviation
Overall	70	328.8	86.7	−93.7	85.6
Age					
55-70	23	341.5	105.0	−98.1	79.4
71-78	23	336.1	77.9	−86.6	97.7
79-90	24	309.7	74.8	−96.2	82.2
Sex					
Male	26	341.7	73.4	−114.1	88.9
Female	44	321.2	93.7	−81.6	82.3
Education					
High School	21	333.5	68.9	−89.9	80.1
> High School	49	326.8	93.9	−95.3	88.6
Body Mass Index					
< 25	24	332.2	77.7	−91.5	70.7
25-29.9	25	322.0	71.6	−104.7	86.1
30+	21	333.0	112.9	−83.1	101.8
Smoking					
Never smoker	27	330.4	95.1	−76.0	87.6
Ever smoker	43	327.8	82.1	−104.8	83.5
Medication					
Bevacizumab	18	318.8	67.3	−78.9	80.9
Ranibizumab	52	332.3	92.8	−98.8	87.4
Genetic Variables^c					
Complement Genes					
CFH: rs1061170 (Y402H)					
TT	14	354.9	66.5	−105.7	64.2
CT	36	334.2	91.0	−96.3	95.5
CC	20	300.8	87.2	−80.5	81.9
CFH: rs1410996					
TT	3	382.0	49.0	−102.3	61.2
CT	16	347.9	98.4	−118.6	80.9
CC	51	319.7	83.6	−85.3	87.9
CFB: rs541862					
TT	64	327.2	89.2	−90.0	87.0

	OCT ^a Central Foveal Thickness at Baseline			Change in OCT Central Foveal Thickness from Baseline to Final	
Variable	N ^b	Mean	Standard Deviation	Mean	Standard Deviation
CT	6	346.2	55.1	-133.3	60.8
C3: rs2230199 (R102G)					
CC	43	313.9	71.3	-92.7	79.7
CG	23	339.1	92.0	-93.7	87.9
GG	4	430.3	148.2	-104.0	151.5
CFI: rs10033900					
CC	21	322.4	72.9	-89.3	82.0
CT	35	331.6	100.5	-91.3	89.1
TT	14	331.4	71.9	-106.1	87.1
Angiogenesis					
VEGFA: rs943080					
CC	14	342.1	114.1	-81.5	110.0
CT	38	326.3	81.4	-112.1	83.9
TT	18	323.8	77.0	-64.2	58.0
TGFBRI: rs334353					
TT	44	332.3	85.2	-99.5	81.5
GT	21	312.3	91.9	-67.5	80.5
GG	5	367.0	77.3	-152.6	119.4
Lipid Pathway					
LIPC: rs10468017					
TT	3	265.0	50.2	-10.3	79.5
CT	28	319.4	66.7	-96.6	75.7
CC	39	340.5	99.1	-97.9	91.3
ABCA1: rs1883025					
CC	40	330.9	92.8	-101.5	84.5
CT	29	326.4	80.6	-83.5	89.0
TT	1	316.0	-	-76.0	-
CETP: rs3764261					
CC	31	335.0	79.0	-89.1	76.6
AC	28	340.3	101.3	-104.3	96.7
AA	11	282.1	50.1	-79.4	84.3
APOC1/APOE: rs4420638					
AA	49	325.9	88.8	-93.8	85.4
AG/GG	21	335.6	83.4	-93.4	88.3
Immune/Inflammatory					
TNFRSF10A: rs13278062					
TT	21	319.2	93.7	-89.4	93.4

	OCT ^a Central Foveal Thickness at Baseline			Change in OCT Central Foveal Thickness from Baseline to Final	
Variable	N ^b	Mean	Standard Deviation	Mean	Standard Deviation
GT	35	333.4	91.3	-87.6	87.8
GG	14	331.6	65.9	-115.5	68.5
SLC16A8: rs8135665					
CC	48	328.6	86.2	-85.8	85.0
CT	20	329.1	88.0	-118.5	86.7
TT	2	329.5	147.8	-34.0	26.9
Extracellular Matrix					
COL8A1: rs13095226					
TT	56	330.8	93.8	-95.4	85.2
CT	14	320.9	50.9	-86.6	90.3
COL10A1: rs1064583					
AA	32	351.8	93.7	-102.6	85.5
AG	25	312.9	69.2	-88.8	82.2
GG	13	302.7	90.8	-81.1	96.7
Other					
ARMS2/HTRA1: rs10490924 (A69S)					
GG	28	306.4	71.2	-76.4	69.3
GT	24	335.8	93.9	-115.2	95.7
TT	18	354.2	94.6	-91.8	92.7
RAD51B: rs8017304					
GG	9	336.1	100.6	-125.6	99.2
AG	31	344.0	97.5	-98.9	92.1
AA	30	310.9	68.3	-78.7	73.3
DDR1: rs3094111					
CC	46	324.9	88.1	-88.1	82.7
CT	20	329.2	90.2	-101.0	98.7
TT	4	372.3	46.7	-121.5	50.7
ADAMTS9/ADAMTS9-AS2: rs6795735					
CC	16	323.1	64.0	-88.9	79.5
CT	33	331.3	103.4	-92.0	98.3
TT	21	329.2	75.5	-99.9	71.0
HSPH1/B3GALT1: rs9542236					
TT	19	345.6	100.3	-118.4	90.8
CT	38	321.6	71.4	-87.8	82.1
CC	13	325.2	108.5	-74.7	86.7

^aOptical coherence tomography (OCT)

^bAll subjects (n=70) have complete data at baseline and final measurements for central foveal thickness (microns) as measured by OCT.

^c Genetic variables are presented in the following order: homozygous for non-risk allele, heterozygous for risk allele, and homozygous for risk allele. The exceptions to this convention are *CFB*: rs541862 and *COL8A1*: rs13095226, presented as homozygous for non-risk allele and heterozygous for risk allele (no subjects were homozygous for risk allele), and *LIPC*: rs10468017 and *RAD51B*: rs8017304, presented as homozygous for protective allele, heterozygous for protective allele, and homozygous for non-protective allele.

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Table 3.

Response to Intravitreal Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration and Associations Between Change in Visual Acuity Over Time and Demographic, Behavioral, and Genetic Characteristics

Variable	N	Slope ^a	Standard Error	P value ^b	P _{het} ^c
Overall	68	-0.085	0.068	0.21	
Age					
55-70	23	-0.326	0.111	0.005	0.07
71-78	23	-0.264	0.355	0.46	
79-90	22	-0.009	0.358	0.98	
Sex					
Male	24	-0.259	0.111	0.02	0.07
Female	44	0.019	0.083	0.82	
Education					
High School	22	0.091	0.118	0.44	0.20
> High School	46	-0.159	0.081	0.06	
Body Mass Index					
< 25	24	-0.107	0.116	0.36	0.82
25-29.9	26	-0.338	0.344	0.33	
30+	18	-0.346	0.371	0.36	
Smoking					
Never	26	0.197	0.102	0.06	<0.001
Ever smoker	42	-0.250	0.080	0.003	
Medication					
Bevacizumab	18	-0.167	0.132	0.21	0.36
Ranibizumab	50	-0.046	0.079	0.56	
Complement Genes^d					P _{trend} ^e
CFH: rs1061170 (Y402H)					
TT	14	-0.499	0.140	0.001	0.03
CT	34	0.055	0.090	0.54	
CC	20	-0.015	0.117	0.90	
CFH: rs1410996					
TT	3	-0.364	0.326	0.27	0.30
CT	15	-0.139	0.146	0.34	
CC	50	-0.041	0.080	0.61	
CFB: rs541862					
TT	61	-0.065	0.072	0.37	0.59
CT	7	-0.187	0.213	0.38	
C3: rs2230199 (R102G)					

Variable	N	Slope ^a	Standard Error	P value ^b	P _{het} ^c
CC	43	-0.088	0.086	0.31	0.69
CG	22	-0.092	0.121	0.45	
GG	3	0.149	0.327	0.65	
CFI: rs10033900					
CC	20	-0.153	0.127	0.23	0.47
CT	33	-0.059	0.099	0.55	
TT	15	-0.018	0.146	0.90	

^aChange in visual acuity over time as measured by the logarithm of the minimum angle of resolution. Positive slope indicates a worsening of acuity, while a negative slope indicates improvement. Improvement from 20/100 to 20/50 over one year would yield a slope of -0.693, while a worsening of acuity from 20/50 to 20/100 would yield a slope of +0.693.

^bPvalue compares the rate of change in visual acuity for each subgroup within each variable versus no change (0).

^cPvalue for heterogeneity: compares the rate of change between groups, assessing whether the subgroups differ from each other for each variable.

^dGenetic variables are presented in the following order: homozygous for non-risk allele, heterozygous for risk allele, and homozygous for risk allele. The exception to this convention is *CFB*: rs541862, presented as homozygous for protective allele and heterozygous for protective allele (no subjects were homozygous for non-protective allele).

^ePtrend reported for genetic variables.

Table 4.

Response to Intravitreal Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration and Associations Between Change in Central Foveal Thickness as Measured By Optical Coherence Tomography Over Time and Demographic, Behavioral, and Genetic Characteristics

Variable	N	Slope ^a	Standard Error	P value ^b	P _{het} ^c
Overall	70	-93.6	10.2	<0.001	
Age					
55-70	23	-98.0	17.6	<0.001	0.54
71-78	23	-103.5	37.2	0.007	
79-90	24	-129.4	37.2	0.001	
Sex					
Male	26	-102.3	16.3	<0.0001	0.32
Female	44	-81.5	12.5	<0.0001	
Education					
High School	21	-89.7	18.2	<0.0001	0.98
> High School	49	-89.1	12.0	<0.0001	
Body Mass Index					
< 25	24	-91.5	17.2	<0.001	0.93
25-29.9	25	-101.2	36.5	0.007	
30+	21	-90.7	37.4	0.02	
Smoking					
Never	27	-76.0	16.0	<0.001	0.29
Ever smoker	43	-97.7	12.7	<0.0001	
Medication					
Bevacizumab	18	-78.7	19.6	<0.001	0.53
Ranibizumab	52	-92.9	11.6	<0.001	
Complement Genes^d					P _{trend} ^e
CFH: rs1061170 (Y402H)					
TT	14	-105.7	22.4	<0.0001	0.39
CT	36	-87.8	14.0	<0.0001	
CC	20	-79.8	18.7	<0.0001	
CFH: rs1410996					
TT	3	-102.3	47.8	0.04	0.15
CT	16	-118.6	20.7	<0.0001	
CC	51	-79.3	11.6	<0.0001	
CFB: rs541862					
TT	64	-85.2	10.3	<0.0001	0.19
CT	6	-131.1	33.5	<0.001	
C3: rs2230199 (R102G)					

Variable	N	Slope ^a	Standard Error	P value ^b	P _{het} ^c
CC	43	-85.3	12.8	<0.0001	0.59
CG	23	-93.7	17.6	<0.0001	
GG	4	-104.0	42.1	0.02	
CFI: rs10033900					
CC	21	-89.3	18.3	<0.0001	0.64
CT	35	-82.6	14.2	<0.0001	
TT	14	-105.4	22.3	<0.0001	

^aSlope: change in central foveal thickness over time as measured by optical coherence tomography, where a positive value indicates an increase and a negative value indicates a decrease in central foveal thickness

^bP value compares the rate of change in central foveal thickness for each subgroup within each variable versus no change (0).

^cP value for heterogeneity: compares the rate of change between groups, assessing whether the subgroups differ from each other for each variable.

^dGenetic variables are presented in the following order: homozygous for non-risk allele, heterozygous for risk allele, and homozygous for risk allele. The exception to this convention is *CFB*: rs541862, presented as homozygous for protective allele and heterozygous for protective allele (no subjects were homozygous for non-protective allele)

^eP for trend reported for genetic variables.

Table 5. Response to Intravitreal Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration and Associations Between Complement Factor H and Complement Factor I Genetic Risk and Change in Visual Acuity and Central Foveal Thickness as Measured by Optical Coherence Tomography Over Time

	Visual Acuity					Central Foveal Thickness				
	N	Slope ^d	Standard Error	P value ^e	P _{het} ^f	N	Slope ^d	Standard Error	P value ^e	P _{het} ^f
<i>CFH</i> risk score ^a										
0-2	24	-0.291	0.110	0.01	0.02	25	-117.5	16.2	<0.001	0.03
3-4	44	0.04	0.082	0.63		45	-73.5	12.1	<0.001	
<i>CFI</i> risk alleles ^b										
0	19	-0.123	0.128	0.04	0.63	50	-87.5	18.9	<0.001	0.86
1-2	49	-0.047	0.079	0.56		20	-91.3	12.0	<0.001	
<i>CFI</i> risk score ^c										
0	60	-0.095	0.071	0.19	0.27	62	-90.2	10.7	<0.001	0.99
1-2	8	0.138	0.195	0.48		8	-90.0	29.9	<0.01	

^aBased on the number of risk alleles for complement factor H (CFH) rs1061170, rs1410996 (0-4)

^bBased on the number of risk alleles for common complement factor I (CFI) variant rs10033900 (0-2)

^cBased on the number of risk alleles for rare CFI variants (0-2)

^dSlope for visual acuity: change in visual acuity over time as measured by the logarithm of the minimum angle of resolution. A positive slope indicates a worsening of acuity, while a negative slope indicates improvement. Improvement from 20/100 to 20/50 over one year would yield a slope of -0.693, while a worsening of acuity from 20/50 to 20/100 would yield a slope of +0.693. The slope presented for a low CFI risk score (0-2 alleles) corresponds to 6.33 ± 2.40 letter improvement in VA using Early Treatment Diabetic Retinopathy Study (ETDRS) acuity, whereas a high CFI risk score (3-4 alleles) corresponds to a -0.85 ± 1.77 letter decline. Slope for central foveal thickness: change in central foveal thickness over time, where a positive value indicates an increase and a negative value indicates a decrease in central foveal thickness.

^eP-value compares the rate of change in visual acuity or central foveal thickness for each subgroup within each variable against no change (0).

^fP-value for heterogeneity: compares the rate of change between groups, assessing whether the subgroups differ from each other for each variable.