Cumulative Effect of Risk Alleles in CFH, ARMS2, and VEGFA on the Response to Ranibizumab Treatment in Age-Related Macular Degeneration

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Purpose: Intravitreal ranibizumab injections currently are the standard treatment for neovascular age-related macular degeneration (AMD). However, a broad range of response rates have been observed, the reasons for which are poorly understood. This pharmacogenetic study evaluated the impact of high-risk alleles in CFH, ARMS2, VEGFA, vascular endothelial growth factor (VEGF) receptor KDR, and genes involved in angiogenesis (LRP5, FZD4) on the response to ranibizumab treatment and on the age of treatment onset. In contrast to previous studies, the data were stratified according to the number of high-risk alleles to enable the study of the combined effects of these genotypes on the treatment response.

Design: Case series study.

Participants: A cohort of 420 eyes of 397 neovascular AMD patients.

Methods: The change in visual acuity (VA) between baseline and after 3 ranibizumab injections was calculated. Genotyping of single nucleotide polymorphisms in the CFH, ARMS2, VEGFA, KDR, LRP5, and FZD4 genes was performed. Associations were assessed using linear mixed models.

Main Outcome Measures: The VA change after 3 ranibizumab injections and the age of neovascular disease onset.

Results: After ranibizumab treatment, AMD patients without risk alleles in the CFH and ARMS2 genes (4.8%) demonstrated a mean VA improvement of 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, whereas no VA improvement was observed in AMD patients with 4 CFH and ARMS2 risk alleles (6.9%; P = 0.014). Patients with 4 high-risk alleles in CFH and ARMS2 were 5.2 years younger than patients with 1 or 2 risk alleles, respectively (63.5%; P<0.0001). The mean age at which the first ranibizumab treatment was carried out among AMD patients with all 6 risk alleles in CFH, ARMS2, and VEGFA was 65.9 years (2%) versus 75.3 years in patients with 0 or 1 high-risk allele (8.8%; P = 0.0001). After ranibizumab treatment, patients with 6 high-risk alleles demonstrated a mean VA loss of 10 ETDRS letters (P<0.0001).

Conclusions: This study evaluated the largest pharmacogenetic AMD cohort reported to date. A cumulative effect of high-risk alleles in CFH, ARMS2, and VEGFA seems to be associated with a younger age of onset in combination with poor response rates to ranibizumab treatment.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.
ber of patients, representing an unparalleled advance in the
treatment of neovascular AMD.8 However, a broad range in
response rates to anti-VEGF therapy has been observed
because some patients showed a better outcome compared
with the average, whereas others showed VA deterioration
instead of improvement. The reasons for different responses
to anti-VEGF treatment are poorly understood.10 Because of
the invasive and time-consuming nature of anti-VEGF ther-
rapy, it is important to understand which factors influence
treatment response. Genetic variation has been recognized
as an important determinant of individual variability of drug
response, and the identification of such variants has en-
hanced patient care—particularly in oncology and cardiol-
ogy.11,12 Knowledge of genetic variants that influence anti-
VEGF therapy may facilitate a personalized treatment
approach for neovascular AMD patients.

During the past decade, the identification of several
gene risk factors involved in AMD has provided impor-
tant insights into the pathogenesis of the disease. The stron-
gest genetic association has been found with a common
variant in the complement factor H (CFH) gene, the main
regulator of the alternative complement pathway.13,14 The
second major genetic risk factor for AMD was identified at
the chromosome 10q26 locus,15 encompassing the age-
related maculopathy susceptibility 2 (ARMS2/LOC387715)
gene and the adjacent high-temperature requirement factor
A1 (HTRA1/PRSS11) gene. Several recent studies suggest
that genetic background may play a role in the varying
response to treatment with ranibizumab.16–18 Conflicting
results have been reported for the role of the CFH gene in
response to ranibizumab treatment. Homozygous carriers of
the 402H high-risk allele in CFH (CC genotype) had a lower
VA outcome in one study16 but a better outcome in an-
other.18 Yet another study concluded that there was no
association between the CFH Y402H genotype and VA
after ranibizumab treatment.17 For ARMS2/HTRA1, one
study reported that heterozygous carriers of the high-risk
HTRA1 allele were associated with better VA outcomes,18
whereas another study presented lower VA outcomes asso-
ciated with the homozygous high-risk ARMS2/HTRA1
genotype.19

To clarify and elaborate on the impact of the high-risk
alleles in CFH and ARMS2 on the treatment with ranibi-
zumab, a multicenter study was conducted that allowed a
thorough analysis in the largest series of neovascular
AMD patients studied to date. Furthermore, the role of
single nucleotide polymorphisms (SNPs) in VEGF-A, in
its receptor VEGFR-2 (KDR), and in genes involved
in angiogenesis and vascularization (LP5 and FZD4) were
analyzed.18 Because individual patients can carry a vari-
able number of high-risk variants, it was hypothesized
that combinations of high-risk alleles may explain the
erogeneity in the age of neovascular disease manifes-
tation and the variable responses to treatment with ranibi-
zumab. Therefore, in contrast to previous studies, the
data were stratified according to the number of high-risk
alleles to enable study of the combined effects of these
genotypes in the development and treatment of neovas-
cular AMD.

Patients and Methods

Study Population

Four hundred twenty eyes of 397 unrelated white patients 50 years
of age or older with active subfoveal CNV secondary to AMD
were evaluated. All study participants were enrolled in
EUGENOA (European Genetic Database), a multicenter database
for the clinical and molecular analysis of AMD, and venous blood
for genotyping was drawn before onset of treatment. One hundred
seventy-two eyes (41%) were examined and treated at the Depart-
ment of Ophthalmology, Radboud University Nijmegen Medical
Centre, Nijmegen, The Netherlands; 193 eyes (46%) were exam-
ined and treated at the Department of Ophthalmology, University
of Cologne, Cologne, Germany; and 55 eyes (13%) were examined
and treated at the Department of Ophthalmology, McGill Univer-
sity Health Center, Montreal, Canada. All participants were en-
rolled between June 2008 and June 2010. The study was performed
in accordance with the tenets of the Declaration of Helsinki (1983
revision) and the Medical Research Involving Human Subjects Act
(WMO). The approval of the local ethics committee was obtained
for all 3 centers, and written, informed consent was acquired from
all participants.

The diagnosis and grading of AMD was based on an interna-
tional classification and grading scheme for age-related macula-
opathy and AMD, as described previously in another study.5 The
diagnosis of active subfoveal CNV secondary to AMD was estab-
lished by retinal specialists based on ophthalmic examination,
fluorescein angiography, and spectral-domain optical coherence
tomography.16–18 Before retinal imaging, pupillary dilatation was
achieved with topical 1.0% tropicamide and 2.5% phenylephrine.
Digital color fundus photography was carried out with Imagenet
(Topcon Corporation, Tokyo, Japan [Nijmegen]), Zeiss FF450 IR
(Carl Zeiss, Jena, Germany), and Canon CF-60 DSI (Canon, Haag-
Streit Deutschland GmbH, Wedel, Germany [Cologne]) digital
fundus cameras. Each participant underwent fluorescein angiogra-
phy with a combined instrument Spectralis HRA + OCT (Heidel-
berg Engineering, Heidelberg, Germany [Nijmegen, Montreal, and
Cologne]) or with Imagenet (Topcon Corporation [Nijmegen]).
The lesion type of the CNV was determined by fluorescein an-
giography and was classified into 4 categories: occult with no
classic lesion, minimally classic lesion, predominantly classic
lesion, and retinal angiomatous proliferation.9,20

Study Design

According to the standard protocol for anti-VEGF therapy, all
patients were treated with 3 initial monthly intravitreal 0.5-mg
ranibizumab injections, followed by on demand reinjections when-
ever signs of CNV activity were detected on funduscopy, spectral-
domain optical coherence tomography, or angiography.21 There-
fore, the follow-up protocol and the total number of injections
varied among patients. Because VA change is maximal after 3
monthly injections,22 and to achieve a comparable and standard-
ized evaluation of the response to ranibizumab treatment, only data
obtained after 3 consecutive ranibizumab injections was used.
Each participant underwent best-corrected VA assessments before
and after treatment with 3 ranibizumab injections. For 347 patients
(81.6%), the Snellen VA measurements were collected retrospec-
tively at a time point after treatment, whereas 78 patients (18.4%)
were followed up prospectively during treatment using Early
Treatment Diabetic Retinopathy Study (ETDRS) VA. Venous
blood samples for the genotyping were collected before onset of
the treatment and before VA measurements were collected retro-
spectively. Patients were excluded from this study if they had
received other prior treatments for active subfoveal CNV second-
ary to AMD. If the second eye became eligible for ranibizumab treatment during the course of the study, then both eyes were included in the study. Age at the first ranibizumab injection was collected, as well as the duration of visual symptoms before the treatment, but this was not available for all patients (n = 218 [52%]). Genotyping of SNPs in the CFH (Y402H; rs1061170), ARMS2 (A69S; rs10490924), VEGFA (rs699947 and rs833069), KDR (rs2071559 and rs7671745), LPR5 (rs3736228), and FZD4 (rs10898563) genes was performed with TaqMan probes and primers using assays developed by Applied Biosystems and an ABI 7900HT system (Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands).

Statistical Analysis
Snellen VA was converted to the logarithm of minimum angle of resolution (logMAR) VA for the purpose of statistical analysis. Change in VA was calculated as the difference between VA at baseline and VA at follow-up. Levene’s test for equality of variances was used to test variability of VA changes between Snellen and ETDRS techniques. The association between genotype and visual response after 3 ranibizumab injections was assessed with linear mixed models using the delta VA as the dependent variable. Association between single genotypes and the age of neovascular disease onset, defined as the age when the first ranibizumab injection was administered, was assessed with linear mixed models using the age of onset as the dependent variable. Relationships were adjusted for significant confounders.

To explore whether a genetic interaction exists between high-risk alleles in CFH (C allele; Y402H) and ARMS2 (T allele; A69S) we stratified the data (the age of onset and delta VA) according to the number of high-risk alleles by creating 4 ‘allele’ groups: (0) patients without high-risk alleles in either gene, (1–2) patients carrying 1 or 2 high-risk alleles, (3) patients carrying 3 high-risk alleles, and (4) patients carrying all four high-risk alleles. Adding other risk alleles to the additive model showed significant results only for the VEGF-A rs699947 polymorphism. Therefore, the data (age of onset and delta VA) were stratified according to the number of high-risk alleles in CFH, ARMS2, and VEGFA by creating 5 allele groups: (0) patients without or with 1 high-risk allele, (1) patients carrying 2 and 3 high-risk alleles, (2) AMD patients carrying 4 high-risk alleles, (3) AMD patients carrying 5 high-risk alleles, and (4) patients carrying all 6 high-risk alleles. Relationships were assessed using linear mixed models and were adjusted for significant confounders. Reported P-values are 2-sided and were considered statistically significant if lower than 0.05. Statistical analyses were performed using SPSS software version 18.0 (SPSS, Inc., Chicago, IL).

Combined Effect of CFH and ARMS2 High-Risk Alleles
The AMD patients who did not carry high-risk alleles in CFH and ARMS2 demonstrated significantly more improvement in VA after ranibizumab treatment compared with carriers of all 4 high-risk alleles in these 2 genes (P = 0.009; Table 2). A mean VA improvement of 10 ETDRS letters was observed in patients without any high risk alleles (n = 20 [4.8%]), 5 ETDRS letters in patients with 1 or 2 risk alleles (n = 267 [63.5%]), and 2.5 ETDRS letters in carriers of 3 risk alleles in CFH and ARMS2 (n = 104 [24.8%]), whereas no mean improvement was observed in patients carrying all 4 high-risk alleles (n = 29 [6.9%]; Fig 1A). A significant association between the number of high-risk alleles in CFH and ARMS2 and the age at the first ranibizumab treatment was observed (P = 0.002; Fig 1B). Carriers of 4 risk alleles in the CFH and ARMS2 genes were 4.4 years younger at treatment onset than the carriers of 3 high-risk alleles (P = 0.006) and 5.2 years younger than the AMD carriers of 1 or 2 risk alleles, respectively (P<0.0001; Table 2).

Combined effect of CFH, ARMS2, and VEGFA High-Risk Alleles
Adding the VEGF rs699947 SNP to the stratification model demonstrated a significant decrease in VA after ranibizumab treatment in the group carrying all 6 high-risk alleles in CFH, ARMS2, and VEGFA compared with the remaining AMD patients. Carriers of all 6 risk alleles demonstrated a mean loss of 10 ETDRS letters after treatment (n = 8 [2%]), whereas all other allele groups demonstrated an improvement in VA after treatment (Fig 2A). In addition, a significant decrease of the age of neovascular onset was observed. The mean age at which the first ranibizumab treatment was carried out among the carriers of all 6 high-risk alleles in CFH, ARMS2, and VEGFA was 65.9 years versus 75.3 years in the AMD carriers of 0 or 1 high-risk allele (n = 35 [8.8%]; P = 0.001; Table 2 and Fig 2B).

Discussion
Pharmacogenetics is the field of study that examines the impact of genetic variation on the response to drugs. As more eye diseases are linked to their underlying genetic defects, pharmacogenetics and genomics will play an increasingly important role in clinical trial design and eventually in everyday ophthalmology practice. Genetic factors are known to play a major role in the pathogenesis of AMD, and it has been suggested that genetic factors also may...
influence response to anti-VEGF treatment in neovascular AMD.\textsuperscript{16–19} This large series of patients evaluated the role of the high-risk alleles in the \textit{CFH}, \textit{ARMS2}, \textit{VEGFA}, \textit{KDR}, \textit{FZD4}, and \textit{LPR5} genes on VA outcome after treatment with ranibizumab injections. Consistent with a previously conducted study, this study demonstrated that carriers of the high-risk \textit{CFH} genotype show less improvement in VA after treatment.\textsuperscript{16}

Table 1. Effect of Genotype on the Visual Acuity Response after 3 Ranibizumab Injections and on the Age When the First Ranibizumab Injection Was Administered

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Mean Visual Acuity Change</th>
<th>P Value</th>
<th>Mean Difference in Age (Standard Error), Years\textsuperscript{\dagger}</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Standard Error), Logarithm of the Minimal Angle of Resolution*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFH rs1261170 (Y402H), n = 420</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>0.105 (0.039)</td>
<td>0.009</td>
<td>+1.70 (1.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>TC</td>
<td>0.031 (0.031)</td>
<td>0.31</td>
<td>+1.13 (0.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>CC</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>ARMS2 rs10490924 (A69S), n = 420</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>0.033 (0.037)</td>
<td>0.37</td>
<td>+0.65 (1.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>GT</td>
<td>0.061 (0.035)</td>
<td>0.28</td>
<td>+2.06 (0.9)</td>
<td>0.026</td>
</tr>
<tr>
<td>TT</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>VEGFA rs699947, n = 400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>0.048 (0.040)</td>
<td>0.23</td>
<td>+0.64 (1.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>CA</td>
<td>0.035 (0.033)</td>
<td>0.29</td>
<td>+1.43 (0.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>CC</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>VEGFA rs833069, n = 393</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>-0.020 (0.044)</td>
<td>0.66</td>
<td>-0.55 (1.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>TC</td>
<td>-0.014 (0.044)</td>
<td>0.74</td>
<td>-0.74 (1.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>CC</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>KDR rs2071559, n = 393</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>0.007 (0.040)</td>
<td>0.86</td>
<td>+0.12 (1.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>GA</td>
<td>-0.064 (0.034)</td>
<td>0.26</td>
<td>+1.84 (0.9)</td>
<td>0.043</td>
</tr>
<tr>
<td>GG</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>KDR rs7671745, n = 388</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>-0.029 (0.049)</td>
<td>0.55</td>
<td>+1.81 (1.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>AG</td>
<td>-0.051 (0.045)</td>
<td>0.27</td>
<td>+0.80 (1.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>AA</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>FZD4 rs1089563, n = 397</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>-0.018 (0.042)</td>
<td>0.67</td>
<td>+1.56 (1.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>AG</td>
<td>-0.040 (0.040)</td>
<td>0.33</td>
<td>+1.06 (1.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>GG</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>LPR5 rs3736228, n = 388</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>-0.011 (0.041)</td>
<td>0.80</td>
<td>0.01 (1.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>CT</td>
<td>-0.002 (0.046)</td>
<td>0.96</td>
<td>0.27 (1.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>CC</td>
<td>0</td>
<td>Reference</td>
<td>0</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*Mean visual acuity improvement in logarithm of the minimum angle of resolution (logMAR) units (0.02 logMAR = 1 Early Treatment Diabetic Retinopathy letter).

\textsuperscript{\dagger}A positive age difference indicates older age and a negative age difference indicates younger age when the first ranibizumab injection was given.

To test the possibility of an additive genetic effect on the response to ranibizumab treatment, the data were stratified according to the number of the high-risk alleles in \textit{CFH}, \textit{ARMS2}, \textit{VEGFA}, or a combination thereof. After stratification for the number of risk alleles in \textit{CFH} and \textit{ARMS2}, the carriers of 4 risk alleles demonstrated no mean VA improvement after 3 injections and required ranibizumab treatment at 5 years younger in age. In AMD patients who also carried 2 \textit{VEGFA} risk alleles, ranibizumab treatment was needed almost 10 years earlier. The \textit{VEGFA} SNP also had an additional negative effect on the VA response rate of ranibizumab. A previous study demonstrated a potential association between the \textit{VEGFA} rs699947 risk genotype and neovascular lesions that remained exudative after several photodynamic therapies. Taking those observations together, the authors conclude that a cumulative effect of high-risk alleles in \textit{CFH}, \textit{ARMS2}, and \textit{VEGFA} may lead to a younger age of onset in combination with worse response rates to ranibizumab treatment. The carriers of 4 high-risk alleles in \textit{CFH}, \textit{ARMS2}, or \textit{VEGFA} demonstrate a better VA improvement than the AMD carriers of 4 high-risk alleles in \textit{CFH} and \textit{ARMS2}, indicating that \textit{CFH} and \textit{ARMS2} genes
have greater consequence on the response to ranibizumab treatment than the VEGFA gene.

Although this study indicates that an additive effect of CFH, ARMS2, and VEGFA genotypes is partially responsible for a decreased response rate to the ranibizumab treatment, the mechanism by which these genotypes interact with anti-VEGF therapy is unknown. Because the anti-VEGF drug is injected locally, it is unlikely that inherited pharmacokinetic effects are responsible for the variation in the concentration of the drug reaching its target. Furthermore, AMD is associated strongly with CFH and ARMS2 polymorphisms, and both genes are related independently to genetic variations. Yet another study showed that it is not the type of neovascularization that is associated with worse visual outcome after ranibizumab treatment, but rather the size of the retinal pigment epithelium area that is affected. Consistent with previous findings, the CNV type did not show an association with response to anti-VEGF treatment in this study population. Conflicting results have been reported concerning an association between CFH and ARMS2/HTRA1 genotypes and the size of the CNV lesion. Nevertheless, further investigation of the mechanism by which these genotypes interact with anti-VEGF therapy is required.

The high-risk genotypes tested in this study are predictive for progression of AMD and response to anti-VEGF treatment, which underlines the potential of genetic screening in predicting the development of end-stage AMD. Identifying high-risk individuals during the early stage of the disease could lead to an awareness of, and more targeted education about, the adoption of a healthy lifestyle and the

### Table 2. Effect of High-Risk Alleles in CFH, ARMS2, and VEGFA on Visual Acuity Response after 3 Ranibizumab Injections and on the Age in Years When the First Ranibizumab Injection Was Administered

<table>
<thead>
<tr>
<th>No. of high-risk alleles in CFH and ARMS2</th>
<th>Mean Visual Acuity Change (Standard Error), Logarithm of the Minimum Angle of Resolution*</th>
<th>P Value</th>
<th>Mean Difference in Age (Standard Error), Years†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.20 (0.08)</td>
<td>0.014</td>
<td>+2.8 (2.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>1 and 2</td>
<td>0.10 (0.06)</td>
<td>0.07</td>
<td>+5.2 (1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>0.05 (0.06)</td>
<td>0.45</td>
<td>+4.4 (1.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>4</td>
<td>0.00</td>
<td>Reference</td>
<td>0.0</td>
<td>Reference</td>
</tr>
<tr>
<td>No. of high-risk alleles in CFH, ARMS2, and VEGFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 and 1</td>
<td>0.40 (0.11)</td>
<td>&lt;0.0001</td>
<td>+9.4 (2.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>2 and 3</td>
<td>0.32 (0.10)</td>
<td>0.001</td>
<td>+7.8 (2.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>4</td>
<td>0.31 (0.10)</td>
<td>0.002</td>
<td>+7.2 (2.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>5</td>
<td>0.29 (0.11)</td>
<td>0.008</td>
<td>+6.9 (2.9)</td>
<td>0.018</td>
</tr>
<tr>
<td>6</td>
<td>0.00</td>
<td>Reference</td>
<td>0.0</td>
<td>Reference</td>
</tr>
</tbody>
</table>

ARMS2 = age-related maculopathy susceptibility 2 gene; CFH = complement factor gene; VEGFA = vascular endothelial growth factor A gene.

*Mean visual acuity improvement in logarithm of the minimum angle of resolution (logMAR) units (0.02 logMAR = 1 Early Treatment Diabetic Retinopathy Study letter).

†Positive age difference indicates older age when the first ranibizumab injection was given.
beneficial use of antioxidants and zinc supplementation in slowing down the progression of AMD.36 Identifying high-risk individuals during advanced stages of the disease could lead to more frequent clinical surveillance in such individuals and could be used for identifying patients for future clinical trials designed to evaluate new treatments. Therapeutic options for late-stage AMD currently are limited; however, this could change in the near future. Ongoing clinical trials currently are testing therapeutic effects of complement inhibition in neovascular and nonexudative AMD.37 One clinical trial is using a combination of intravitreal therapy of anti-C5-aptamer (ARC1905) and ranibizumab.37 Those AMD patients with high-risk genotypes and decreased response rates to ranibizumab treatment may demonstrate greater benefit from a combination therapy with complement inhibition and anti-VEGF. A limitation of

Figure 1. Graphs showing the cumulative effect of complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) risk alleles on (A) the change in visual acuity (VA) after ranibizumab treatment and (B) on the age of neovascular onset. A, Visual acuity change after 3 ranibizumab injections from baseline (y-axis, 0.20 corresponds to 10 Early Treatment Diabetic Retinopathy Study letters, a positive change indicates VA gain, and a negative change indicates VA loss) clustered by a CFH and ARMS2 allelic composition (x-axis): (4) participants carrying all 4 high-risk alleles (n = 29 [6.9%]), (3) patients with 3 high-risk alleles (n = 104 [24.8%]), (2-1) patients carrying 1 or 2 risk alleles (n = 267 [63.5%]), and (0) participants without high-risk alleles in either genes (n = 20 [4.8%]). The carriers of all 4 CFH and ARMS2 high-risk alleles demonstrated a significantly lower mean VA than the age-related macular degeneration (AMD) patients carrying 2, 1, or no high-risk CFH and ARMS2 alleles. B, The age when first ranibizumab injection has been administered (y-axis) clustered by CFH and ARMS2 allelic composition as mentioned above. The carriers of all 4 alleles in CFH and ARMS2 received their first ranibizumab injection at a significantly younger age, indicating that those high-risk genes lead to an earlier onset of neovascular AMD. logMAR = logarithm of the minimum angle of resolution.

Figure 2. Graphs showing the cumulative effect of complement factor H (CFH), age-related maculopathy susceptibility 2 (ARMS2), and vascular endothelial growth factor A (VEGFA) high-risk alleles (A) on the change in visual acuity (VA) after ranibizumab treatment and (B) on the age of neovascular onset. A, Visual acuity change after 3 ranibizumab injections from baseline (y-axis, 0.20 corresponds to 10 Early Treatment Diabetic Retinopathy Study letters, a positive change indicates VA gain, and a negative change indicates VA loss) clustered by CFH, ARMS2, and VEGFA allelic composition (x-axis): (6) patients carrying all 6 high-risk alleles (n = 8 [2%]), (5) age-related macular degeneration (AMD) patients carrying 5 risk alleles (n = 33 [8.3%]), (4) participants with 4 risk alleles (n = 116 [29%]), (3-2) patients carrying 3 or 2 risk alleles (n = 208 [52%]), and (1-0) patients carrying 1 or no high-risk alleles in CFH, ARMS2, and VEGFA genes (n = 35 [8.8%]). Compared with the remaining AMD patients, the carriers of all 6 high-risk alleles demonstrated a significant worsening of VA. B, Age when the first ranibizumab injection was administrated (y-axis) clustered by CFH, ARMS2, and VEGFA allelic composition as mentioned above. Adding the VEGFA high-risk allele to the stratification model demonstrated a younger age at which the first ranibizumab treatment was carried out compared with the stratification model based on CFH and ARMS2 risk alleles. The mean age among the carriers of all 6 high-risk alleles in CFH, ARMS2, and VEGFA was 65.9 years versus 75.3 years in the AMD carriers of no or 1 high-risk alleles (P = 0.001). logMAR = logarithm of the minimum angle of resolution.
the study is that the conclusions are based on a limited number of AMD patients with 4 or 6 high-risk alleles in CFH, ARMS2, and VEGFA genes. Therefore, these results should be validated in other patient cohorts. The vast majority of patients are in the middle of the distribution, and a wide range in response to ranibizumab treatment was observed among allele groups, indicating that other factors also contribute to the response rate. Additional studies of the effect of phenotypic and environmental parameters, additional genetic variants, and possibly proteomic profiling may lead to a more accurate prediction model, which would provide the basis for personalized medicine for treatment of neovascular AMD.

In conclusion, these findings demonstrate a cumulative effect of high-risk alleles, leading to a younger age of neovascular AMD onset in combination with poor response rates to intravitreal ranibizumab treatment. Because genetic variation partially explains the wide range of response to ranibizumab treatment, genetic screening has the potential to identify high-risk individuals and in future may help clinicians to tailor medical care to individual needs.

References


Footnotes and Financial Disclosures

Supported by the Netherlands Organization for Scientific Research, The Hague, the Netherlands (grant no. 016.096.309); the MD Fonds, Utrecht, the Netherlands; Oogfonds, Utrecht, the Netherlands; Landelijke Stichting voor Blinden en Slechtzienden, Utrecht, the Netherlands; Algemene Nederlandse Vereniging ter Voorkoming van Blindheid, Doorn, the Netherlands; Stichting A.F. Deutman Oogheelkunde Researchfonds, Nijmegen, the Netherlands; Stichting Nederlands Oogheelkundig Onderzoek, Rotterdam, the Netherlands; Stichting Blindenhulp, Den Haag, the Netherlands; the Gelderse Blindenstichting, Velp, the Netherlands; Nijmeegse Oogzorgstichting Stichting, Nijmegen, the Netherlands; the Foundation Fighting Blindness Canada, Toronto, Canada; and by the Koeln Fortune Program/Faculty of Medicine, University of Cologne, Cologne, Germany.

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