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ASSOCIATION BETWEEN HIGH-RISK DISEASE LOCI AND RESPONSE TO ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR WET AGE-RELATED MACULAR DEGENERATION

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Abstract

Purpose: To investigate whether there is an association between known age-related macular degeneration genetic risk variants in the *CFH*, *ARMS2*, and *HTRA1* genes and response to anti-vascular endothelial growth factor (VEGF) (ranibizumab or bevacizumab) treatment for wet age-related macular degeneration.

Methods: A retrospective review of 150 patients with documented wet age-related macular degeneration based on clinical examination and fluorescein angiogram was performed. Patients received anti-VEGF therapy with ranibizumab and/or bevacizumab. Patients were genotyped for the single-nucleotide polymorphism rs1061170, rs10490924, rs3750848, rs3793917, rs11200638, and rs932275 and for the indel del443ins54 spanning the *CFH*, *ARMS2*, and *HTRA1* genes.

Results: There were 57 patients who were characterized as negative responders to anti-VEGF therapy, and 93 patients who were characterized as positive responders. There was no significant difference in mean baseline visual acuity between the groups. Negative responders were followed for a mean duration of 24.0 months, while positive responders were followed for a mean duration of 22.0 months. Although the frequency of the at-risk alleles was higher in the positive responders when compared with the negative responder, this did not reach statistical significance.

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Additionally, there was no significant association between genotype and the number of injections or absolute change in visual acuity in both groups of responders.

Conclusion: In our patient cohort, there was no statistically significant association between response to anti-VEGF therapy and the genotype in both positive-responder and negative-responder groups. Larger studies with more power are necessary to further determine whether a pharmacogenetic association exists between wet age-related macular degeneration and anti-VEGF therapy.

Keywords

age-related macular degeneration; genetics; pharmacogenetic response

Age-related macular degeneration (AMD) is a leading cause of visual impairment in individuals older than 55 years in the developed countries[1–3] and has caused more than 30 million people to become blind worldwide.[3] The major risk factors for AMD include age and smoking, with age being the strongest risk factor. In addition to environmental factors, familial[4,5] and twin[6] studies have confirmed that genetic factors play a substantial role in the etiology of AMD and in the variation of its overall severity.[6] One of the first significant breakthroughs in the understanding of the genetics of AMD came in 2005 with the identification of a strong association between the disease and variants in the complement factor H (*CFH*) gene on Chromosome 1.[7–10] Specifically, the rs1061170 single-nucleotide polymorphism (SNP) in the *CFH* gene results in a thymine-to-cytosine (T → C) transition and has been found to be highly associated with AMD in multiple populations.[11,12]

Through family linkage studies and fine mapping, a second major genetic association with AMD has been localized in Chromosome 10, region q26, centered around 2 nearby genes: *ARMS2* (age-related maculopathy susceptibility 2) and *HTRA1* (high-temperature requirement factor A1).[13–15] Both *HTRA1* and *ARMS2* have been shown to be expressed in the retina. Six risk alleles involving the *ARMS2*/*HTRA1* region (rs10490924, rs3750848, del443ins54, rs3793917, rs11200638, and rs932275) are associated with AMD and reside on a single high-risk haplotype.[15,16] The rs10490924 SNP encodes a nonsynonymous A69S mutation in *ARMS2* via a guanine-to-cytosine (G → C) transition. The deletion allele of an insertion/deletion (indel) variant in the 3′ untranslated region of the *ARMS2* gene, del443ins54, destabilizes the messenger RNA transcript of the *ARMS2* gene leading to its rapid decay.[16] The rs11200638 SNP, located in the *HTRA1* promoter region, is thought to affect the expression of *HTRA1*.[13,17] Given the strong linkage disequilibrium across the region, the identity of which gene, *HTRA1* or *ARMS2*, causes disease susceptibility has been contro-versial[16] because the location of the causal variant is unclear.

Recently, investigators have attempted to determine whether an individual's genetic background plays a role in the response to AMD treatment. While looking at the effect of nutritional supplementation on AMD progression, Klein et al[18] demonstrated that an individual's response to zinc might be related to their *CFH* genotype. Feng et al,[19] revealed an association between photodynamic therapy and C-reactive protein genetic variants, but no association was observed between photodynamic therapy and *CFH* genetic variants.

However, Brantley et al[20] did observe a response between photodynamic therapy and the *CFH* Y402H genotype but not with the rs10490924 SNP in the *ARMS2* gene.

The treatment of wet AMD has been drastically improved with the addition of anti-vascular endothelial growth factor (anti-VEGF) therapy. Ranibizumab is currently approved for the treatment of wet AMD, and bevacizumab has shown much promise.[21,22] Brantley et al[23] demonstrated that the *CFH* at risk C allele was associated with a worse response to bevacizumab treatment than was the T allele. A pharmacogenetic relationship was not observed between bevacizumab treatment and the rs10490924 variant in the *ARMS2* gene. Furthermore, Lee et al[24] demonstrated an association between the *CFH* Y402H risk allele and the number of ranibizumab injections, although postinjection visual acuities were not influenced by genotype.

It is unclear whether definitive associations between the major AMD genetic risk variants and anti-VEGF treatment exist, and more evidence is necessary. Further studies of the pharmacogenetic relationship with anti-VEGF therapy are necessary to determine if genotype can influence treatment outcome. There are only a few small reports studying this relationship with variants in the *CFH* and *ARMS2* genes,[21,23,24] and there are no published reports assessing the influence of the *HTRA1* gene. In this work, we seek to determine whether there is an association between the genetic variants in the *CFH*, *ARMS2*, and *HTRA1* genes and response to anti-VEGF (ranibizumab or bevacizumab) treatment for wet AMD.

Methods

Patients

This retrospective cohort study was approved by the Institutional Review Board of the Wills Eye Institute and the Mid Atlantic Retina associates. All subjects provided signed informed consent before participation. The research adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with the Health Insurance Portability and Accountability Act regulations. All individuals were recruited from the retina practices of the Wills Eye Hospital and the Mid Atlantic Retina practices and had a clinical examination by a retina specialist.

Those with macular changes were classified based on AREDS (Age-Related Eye Disease Study) Report 6,[25] which we modified to allow grading of our subjects by funduscopic appearance during examination by a retina specialist. Patients were examined for the presence of drusen (appearance and size), pigmentary abnormalities, geographic atrophy, and choroidal neovascularization. When a choroidal neovascularization lesion was suspected, fluorescein angiography was performed to confirm its presence. Blood samples were taken from all subjects for genotyping.

Initially, patients were treated with injections at monthly intervals for at least 3 months. The interval between injections was gradually increased as long as the optical coherence tomography remained stable and dry. We reviewed the medical reports of 298 patients with documented wet AMD and choroidal neovascularization lesions. Eyes with macular scars at

baseline were excluded from the study, as were those received previous photodynamic therapy, pegaptanib sodium, or focal laser treatment. Eyes were followed for a minimum of 3 months after receiving the first anti-VEGF injection to be included in the study. After reviewing the medical reports, 150 of 298 patients were included in the study, 16 of whom contributed both eyes. Measurement of visual acuity for all patients was assessed by Snellen charts. Patients were defined as positive responders and negative responders after anti-VEGF (ranibizumab or bevacizumab) therapy as follows: Positive responders were defined as patients who at the final visit had either an improvement or no change in visual acuity compared with baseline in at least one eye, providing that the most recent visual acuity was ≥ 20/200. Negative responders were defined as patients who lost visual acuity when compared with baseline or had a final visual acuity <20/200. Of 16 patients whose both eyes were included, 5 did not respond in either eye, 7 responded in both eyes, and the remaining 4 responded in 1 eye but not the other.

Genotype Determination

Patients were genotyped for the SNPs rs1061170, rs10490924, rs3750848, rs3793917, rs11200638, and rs932275 and for the indel del443ins54 spanning the *CFH*, *ARMS2*, and *HTRA1* genes. The 6 SNPs were genotyped with a commercially available genotyping TaqMan assay, while we used polymerase chain reaction to validate the existence of indel del443ins54 in the 3′ untranslated region of the *ARMS2* gene, as previously described.[26]

Data Analysis

The nominal significance of association for each demographic and clinical variable was calculated using the *t*-test for means with continuous data (e.g., age, number of injections, and visual acuity) and the χ^2 test for categorical data (e.g., gender) in the R language and environment for statistical programming.[27] The PLINK tool set for whole-genome association[28] was used to perform the χ^2 test for allelic association, logistic regression for genotypic association at each locus on the observed response to treatment, and the Wald test for association with quantitative traits (number of injections required at follow-up and absolute change in visual acuity). *P* values were not corrected for multiple comparisons, and nominal *P* values were reported.

Results

We evaluated 150 patients with AMD who were treated with anti-VEGF therapy (ranibizumab or bevacizumab) across 7 known genetic risk factors (6 SNPs and 1 choroidal neovascularization) for AMD. Positive and negative responders were matched for age, gender, duration and amount of treatment, and pre-treatment and posttreatment acuities; the only statistically significant difference between the groups was the posttreatment visual acuity and mean age (Table 1). Negative responders were significantly older than positive responders on average (82.16 ± 0.86 years vs. 79.60 ± 0.82 years, respectively; $P \leq 0.03$). All other factors were well matched ($P \leq 0.28$). As expected, postinjection visual acuity was significantly improved in positive responders when compared with negative responders (1.31 ± 0.08 logarithm of the minimum angle of resolution [logMAR] vs. 0.43 ± 0.03 logMAR, respectively; $P \leq 1.05 \times 10^{-15}$).

Ninety-three patients (62%) had a positive response to treatment; however, this response was not significantly associated with any of the risk variants (Table 2). Of the 7 SNPs analyzed, the risk allele frequency in both positive responders and negative responders was highest with rs1061170 (0.55 and 0.50, respectively), the SNP encoding a nonsynonymous Y402H substitution in the *CFH* gene. Of the 6 SNPs analyzed in the *ARMS2-HTRA1* locus on Chromosome 10, the risk allele frequency in positive responders ranged from 0.41 to 0.43, and in negative responders from 0.39 to 0.41. By odds ratio, all AMD risk alleles had a higher frequency in the positive-responder group and appeared to increase the effect of anti-VEGF treatment, although this effect was not statistically significant. The largest effects were seen at rs1061170 (Y402H in *CFH*; $P \leq 0.45$; odds ratio = 1.20), closely followed by rs3750848 (intron in *ARMS2*; $P \leq 0.48$; odds ratio = 1.19). Other loci showed a less appreciative effect on response to anti-VEGF treatment (odds ratio ranged from 0.99 to 1.10).

Finally, we did not find a significant association between subjects' genotype and the treatment response, the number of injections required at follow-up, or the absolute change in visual acuity (Table 3).

Discussion

Although the various polymorphisms in the *CFH* (rs106117) and *ARMS2*/*HTRA1* (rs10490924, rs3750848, del443ins54, rs3793917, rs11200638, rs932275) genes have consistently been shown to be associated with AMD, we did not find a statistically significant pharmacogenetic association between these SNPs and the efficacy of anti-VEGF therapy with ranibizumab or bevacizumab. We also found no statistically significant difference in the frequency of the risk polymorphisms between positive responders and negative responders to anti-VEGF therapy. Furthermore, a stepwise multivariate linear regression failed to show a significant epistatic interaction effect among all the seven variants (data not shown).

Both responder groups were well matched for features including gender, duration of treatment, and baseline visual acuity evidenced by the lack of a statistically significant difference between positive responders and negative responders with regards to these factors. However, negative responders were significantly older than positive responders on average (82.16 ± 0.86 years vs. 79.60 ± 0.82 years, respectively; $P \leq 0.03$), and although not significantly different, they presented with worse baseline visual acuity (0.89 ± 0.08 logMAR vs. 0.79 ± 0.05 logMAR respectively; $P \leq 0.28$). Furthermore, a joint modeling of age and genotype by linear regression failed to achieve statistical significance at any locus (data not shown), suggesting that age does not have an effect on response to treatment when genetics are considered. In this study, we may not have the power to detect significantly different baseline visual acuities between the responder groups. However, it is possible that negative responders presented with either more advanced or more aggressive disease and thus had less response to treatment, potentially negating any pharmacogenetic response.

Because the SNPs tested in our cohort are known to be associated with AMD, it is not surprising to find higher allele frequencies in our sample compared with the general

population. In terms of genotypic risk, Brantley et al[23] demonstrated that at a mean follow-up of 9.33 months, 10.5% of patients harboring a homozygous risk allele genotype (CC) at the *CFH* Y402H locus showed an improvement with bevacizumab treatment compared with 53.7% of heterozygotes (CT) and wild-type homozygotes (TT), showing a statistically significant difference ($P \leq 0.004$). In comparison, our study had a longer follow-up period on average (24.02 ± 1.51 months in the negative-responder group and 22.00 ± 1.22 months in the positive-responder group) and found that 60.7% of patients harboring a homozygous risk allele genotype (CC) at the *CFH* Y402H locus showed visual improvement with anti-VEGF treatment compared with 62.9% of heterozygotes (CT) and wild-type homozygotes (TT), although the result was not significant ($P \leq 0.91$ by χ^2, data not shown). Lee et al[24] reported an increase in the *CFH* Y402H risk allele frequency with more ranibizumab injections during follow-up, although postinjection visual acuities were not affected by one's genotype. Our results confirm that posttreatment visual acuities are not significantly associated with a subject's genotypes, but our results failed to replicate the previously reported association between genotype and the number of anti-VEGF injections.

In summary, in contrast to Brantley et al,[20] our results do not show a significant association between the SNPs tested and response to anti-VEGF treatment for AMD. Also, in contrast to Lee et al,[24] we found that the mean number of injections required is not affected by the genotype. We performed a retrospective study, which included a modest sized patient cohort. It is possible that with a larger patient population, significant associations between various SNPs and response to treatment could be detected. We also arbitrarily defined a positive responder and negative responder to anti-VEGF therapy, based on the expertise and experience of the various retina specialists. Lee et al[24] applied the mean change in logMAR acuity according to each genotype to assess pharmacologic response, but we used the qualitative responder/nonresponder trait for the analysis. We believe that our design is a more reasonable approach considering that our study is focused on individual response to anti-VEGF and not on mean group response to anti-VEGF.

To conclude, we evaluated the potential association between selected SNPs in the *CFH*, *ARMS2*, and *HTRA1* genes, and response to anti-VEGF (ranibizumab or bevacizumab) treatment for wet AMD. In our patient population, there was no statistically significant difference in the frequency of the at-risk polymorphisms between the positive and negative responders to anti-VEGF therapy, and we do not believe that the management of wet AMD should be guided by ones genotype at this time. Because of the limitations of this retrospective study, a larger prospective study with more power should be designed to assess the presence of a pharmacogenetic relationship between anti-VEGF treatment of AMD and high-risk disease alleles.

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References

1. Bressler NM, Bressler SB, Congdon NG, et al. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. Arch Ophthalmol 2003;121:1621–1624. [PubMed: 14609922]
2. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477–485. [PubMed: 15078664]
3. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844–851. [PubMed: 15640920]
4. Heiba IM, Elston RC, Klein BE, Klein R. Sibling correlations and segregation analysis of age-related maculopathy: the Beaver Dam Eye Study. Genet Epidemiol 1994;11:51–67. [PubMed: 8013888]
5. Seddon JM, Ajani UA, Mitchell BD. Familial aggregation of age-related maculopathy. Am J Ophthalmol 1997;123: 199–206. [PubMed: 9186125]
6. Seddon JM, Cote J, Page WF, et al. The US twin study of age-related macular degeneration: relative roles of genetic and environmental influences. Arch Ophthalmol 2005;123:321–327. [PubMed: 15767473]
7. Edwards AO, Ritter R III, Abel KJ, et al. Complement factor H polymorphism and age-related macular degeneration. Science 2005;308:421–424. [PubMed: 15761121]
8. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A 2005;102:7227–7232. [PubMed: 15870199]
9. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science 2005;308:419–421. [PubMed: 15761120]
10. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. Science 2005;308:385–389. [PubMed: 15761122]
11. Souied EH, Leveziel N, Richard F, et al. Y402H complement factor H polymorphism associated with exudative age-related macular degeneration in the French population. Mol Vis 2005; 11:1135–1140. [PubMed: 16379025]
12. Zareparsi S, Branham KE, Li M, et al. Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. Am J Hum Genet 2005;77:149–153. [PubMed: 15895326]
13. Dewan A, Liu M, Hartman S, et al. HTRA1 promoter polymorphism in wet age-related macular degeneration. Science 2006;314:989–992. [PubMed: 17053108]
14. Jakobsdottir J, Conley YP, Weeks DE, et al. Susceptibility genes for age-related maculopathy on chromosome 10q26. Am J Hum Genet 2005;77:389–407. [PubMed: 16080115]
15. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. Hum Mol Genet 2005;14:3227–3236. [PubMed: 16174643]
16. Fritsche LG, Loenhardt T, Janssen A, et al. Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA. Nat Genet 2008;40:892–896. [PubMed: 18511946]
17. Yang Z, Camp NJ, Sun H, et al. A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. Science 2006;314:992–993. [PubMed: 17053109]
18. Klein BE, Knudtson MD, Lee KE, et al. Supplements and age-related eye conditions: the Beaver Dam Eye Study. Ophthalmology 2008;115:1203–1208. [PubMed: 17997484]
19. Feng X, Xiao J, Longville B, et al. Complement factor H Y402H and C-reactive protein polymorphism and photodynamic therapy response in age-related macular degeneration. Ophthalmology 2009;116:1908–1912 e1. [PubMed: 19692124]
20. Brantley MA Jr, Edelstein SL, King JM, et al. Association of complement factor H and LOC387715 genotypes with response of exudative age-related macular degeneration to photodynamic therapy. Eye (Lond) 2009;23:626–631. [PubMed: 18292785]
21. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006;113:363–372 e5. [PubMed: 16458968]

22. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006; 26:383–390. [PubMed: 16603955]

23. Brantley MA Jr, Fang AM, King JM, et al. Association of complement factor H and LOC387715 genotypes with response of exudative age-related macular degeneration to intravitreal bevacizumab. Ophthalmology 2007;114: 2168–2173. [PubMed: 18054635]

24. Lee AY, Raya AK, Kymes SM, et al. Pharmacogenetics of complement factor H (Y402H) and treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol 2009;93:610–613. [PubMed: 19091853]

25. Ferris FL, Davis MD, Clemons TE, et al. A simplified severity scale for age-related macular degeneration: AREDS report no. 18. Arch Ophthalmol 2005;123:1570–1574. [PubMed: 16286620]

26. Hadley D, Orlin A, Brown G, et al. Analysis of six genetic risk factors highly associated with AMD in the region surrounding ARMS2 and HTRA1 on chromosome 10, region q26. Invest Ophthalmol Vis Sci 2010;51:2191–2196. [PubMed: 19933195]

27. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2010.

28. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–575. [PubMed: 17701901]

Table 1.

Demographic and Clinical Summaries of Positive Responders Versus Negative Responders

Variable	Negative Responder (n = 57)	Positive Responder (n = 93)	*P*
Mean age (range), years	82.16 ± 0.86 (61–94)	79.60 ± 0.82 (60–93)	0.03
Number of men (frequency)	18 (0.33)	30 (0.31)	0.93
Mean duration follow-up (range), months	24.02 ± 1.51 5.00–46.50	22.00 ± 1.22 (3.39–48.5)	0.30
Mean number of injections	10.26 ± 0.84	9.80 ± 0.62	0.66
Bevacizumab	5.21 ± 0.60	5.19 ± 0.51	0.98
Ranibizumab	5.05 ± 0.69	4.60 ± 0.54	0.61
Mean preinjection VA (Snellen VA)	0.89 ± 0.08 (20/155)	0.79 ± 0.05 (20/123)	0.28
[range Snellen VA], logMAR	[CF-20/25]	[CF-20/25]	
Mean postinjection VA (Snellen VA)	1.31 ± 0.08 (20/408)	0.43 ± 0.03 (20/53)	1.56×10^{-15}
[range Snellen VA], logMAR	[LP-20/30]	[20/200–20/20]	

values are represented as either the mean ± the standard error (for age duration of treatment, total number of injections, pre and post injection visual acuity) or raw counts with frequency (for number of men) in positive responders versus negative responders.

VA, visual acuity; CF, counting fingers; LP, light perception.

Table 2.

Single Marker Allelic Association of Response to Anti-VEGF Treatment of Patients With AMD

Marker	Chr	Gene	Relative Position	Risk Allele	Wild-Type Allele	Freq Pos	Freq Neg	*P*	Odds Ratio
rs1061170	1	CFH	Y402H	C	T	0.55	0.50	0.45	1.20
rs10490924	10	ARMS2	A69S	T	G	0.42	0.41	0.81	1.06
rs3750848	10	ARMS2	Intron	G	T	0.43	0.39	0.48	1.19
del443ins54	10	ARMS2 3′	untranslated region	2	1	0.42	0.40	0.70	1.10
rs3793917	10	—	Intergenic	G	C	0.41	0.41	0.95	1.02
rs11200638	10	HTRA1	Promoter	A	G	0.41	0.41	0.97	0.99
rs932275	10	HTRA1	Intron	A	G	0.41	0.39	0.79	1.07

1, no indel for AMD; 2, indel for AMD; freq pos, frequency of the risk alleles in cases; freq neg, frequency of the risk alleles in controls.

Table 3.

Single Marker Significance of Association Across Different Predictors

Marker	Risk Allele	Wild-Type Allele	Genotype for Positive Responders	Genotype for Negative Responders	Allelic *P*	Total Inj *P*	ΔVA *P*
rs1061170	C	T	27/42/19	15/25/15	0.47	0.95	0.25
rs10490924	T	G	21/37/35	10/26/20	0.82	0.38	0.43
rs3750848	G	T	20/36/32	9/24/21	0.50	0.82	0.64
del443ins54	2	1	22/35/36	10/25/21	0.72	0.26	0.41
rs3793917	G	C	19/38/35	10/25/20	0.95	0.33	0.32
rs11200638	A	G	19/38/36	11/24/21	0.97	0.38	0.29
rs932275	A	G	20/36/37	10/24/22	0.80	0.49	0.48

P value of significance by genotypic association on response by χ^2 test, genotypic association on total number of injections, and on change in visual acuity by logistic regression are indicated.

1, no indel for AMD; 2, indel for AMD.