Pharmacogenetics and Age-Related Macular Degeneration

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Pharmacogenetics seeks to explain interpatient variability in response to medications by investigating genotype-phenotype correlations. There is a small but growing body of data regarding the pharmacogenetics of both nonexudative and exudative age-related macular degeneration. Most reported data concern polymorphisms in the \textit{complement factor H} \((\text{CFH})\) and \textit{age-related maculopathy susceptibility} \((\text{ARMS2})\) genes. At this time, the data are not consistent and no definite conclusions may be drawn. As clinical trials data continue to accumulate, these relationships may become more apparent.

1. Introduction

Pharmacogenetics, an evolving research discipline within ophthalmology, investigates genotype-phenotype correlations in an attempt to explain interpatient variability in response to medications. While the earliest ophthalmic pharmacogenetic reports involved the treatment of open-angle glaucoma \([1, 2]\), there is now a growing body of data concerning various treatments for age-related macular degeneration (AMD).

The combination of antioxidants and zinc studied by the Age-Related Eye Disease Study (AREDS) was reported to reduce disease progression and visual loss in certain patients with nonexudative AMD \([3]\). These supplements remain the only clinically proven treatment for nonexudative AMD. A variety of treatments have demonstrated efficacy in the treatment of choroidal neovascularization (CNV) secondary to exudative AMD, including photodymanic therapy (PDT) with verteporfin (Visudyne, Novartis, Basel, Switzerland) and the antivascular endothelial growth factor (VEGF) agents. Currently, there are three anti-VEGF agents in clinical use in the US: pegaptanib (Macugen, Eyetech, Palm Beach Gardens, Fla) \([4]\), ranibizumab (Lucentis, Genentech, South San Francisco, Calif) \([5, 6]\), and bevacizumab (Avastin, Genentech, South San Francisco, Calif) \([7]\). Despite the overall efficacy of these treatments, there remains a persistent and unexplained variability in treatment response with certain patients, especially those treated with anti-VEGF agents \([8]\). Intravitreal triamcinolone acetonide has been reported to show some efficacy as an adjunctive therapy in some patients with CNV, especially when combined with PDT \([9]\) or bevacizumab \([10]\). Unfortunately, elevation of intraocular pressure is an important adverse event associated with this treatment \([11]\).

Pharmacogenetics may help to explain some of this variability in treatment efficacy and toxicity.

2. Studied Genotypes

The complement system appears to play an important role in the pathogenesis of AMD \([12]\). Recent studies demonstrated that a single nucleotide polymorphism (SNP) in the complement factor H \((\text{CFH})\) gene is strongly linked with AMD \([13–16]\). As a primary regulator of the complement cascade, CFH plays an important role in innate immunity and inflammatory response. In these studies, individuals with one risk allele for this SNP (genotype TC) had a significantly increased risk of AMD (odds ratios (ORs) ranging from 2.5 to 4.6), and two risk alleles (genotype CC) conferred a correspondingly higher risk (ORs ranging from 3.3 to 7.4). Multiple reports have confirmed this
association in different populations [17–21]. The influence of the complement pathway on AMD was further validated when polymorphisms in the complement factor B/C2 (CFB), C3, factor I (FI), and CFH-related proteins 1 and 3 were also shown to influence AMD susceptibility [22–27]. A second locus, encompassing the ARMS2 (age-related maculopathy susceptibility 2, also called LOC387715) and HTRA1 (HtrA serine peptidase 1) genes on chromosome 10q26, has also been consistently associated with AMD [28–31]. It has proven difficult to determine whether variants in ARMS2 or HTRA1 are responsible for the association with AMD because they are in strong linkage disequilibrium and their effects are statistically indistinguishable. The function of the ARMS2 protein is unknown. There is some evidence that the HTRA1 polymorphism is functional and influences gene expression, but these data have been inconsistent, and this continues to be debated [32–38]. Polymorphisms in numerous other genes may exert smaller effects on AMD susceptibility. Two recent genome-wide association studies (GWAS) showed that the hepatic lipase (LIPC) and tissue inhibitor of metalloprotease 3 (TIMP3) genes may influence AMD risk [39, 40]. Apolipoprotein E levels, encoded by APOE, also have been associated with AMD [41]. Although VEGF (also known as VEGFA) has not been reported to be a major AMD susceptibility locus, polymorphisms within this gene have been associated with exudative AMD in some studies [42, 43]. Similarly, VEGF receptor 2, encoded by kinase insert domain receptor (KDR), may play a role in the development of CNV [44]. Plasma levels of C-reactive protein, encoded by C-reactive protein (CRP), have been associated with AMD [45, 46]. Low-density lipoprotein receptor-related protein 5 (LRP5) and frizzled homolog 4 (FZD4) have been associated with retinal vascularization but not specifically with AMD [47]. Pigment epithelium-derived factor (PEDF) polymorphisms have also been studied in AMD patients [48]. The glucocorticoid receptor gene (GR) has six well-studied polymorphisms: ER22/23EK [49], N363S [50], Bcl [51], N766N, a substitution within intron 3, and a substitution within intron 4 [52]. None of these SNPs is reported to represent an AMD susceptibility locus, but several have been associated with altered sensitivity to glucocorticoids in nonphthalmic studies.

### 3. Pharmacogenomics of AREDS Vitamins

A subset of patients studied in the AREDS trials was evaluated for a pharmacogenetic response with respect to polymorphisms in CFH Y402H and ARMS2/LOC387715 A69S (Table 1). A total of 264 of 876 AREDS category 3 and 4 patients (30.1%) progressed to advanced AMD over five years. In these patients, the CFH TT genotype was associated with a significantly more favorable treatment response than was the CFH CC genotype. Specifically, AREDS supplementation was associated with a greater reduction in AMD progression (68%) in those with the low-risk TT genotype compared with those with the high-risk CC genotype (11%) [53]. No significant associations with AMD progression were seen for the ARMS2 A69S variant.

### Table 1: Pharmacogenetics of AREDS vitamins and intravitreal triamcinolone acetonide.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Genes</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS vitamins</td>
<td>CFH and ARMS2</td>
<td>CFH TT associated with greater reduction in disease progression; no effect with ARMS2 [53]</td>
</tr>
<tr>
<td>IVTA</td>
<td>Multiple</td>
<td>No association between IOP elevation and any gene [54]</td>
</tr>
</tbody>
</table>

### 4. Pharmacogenetics of PDT

Several studies have investigated the relationship between genetic variants and response to PDT (Table 2). The majority of these have focused on the AMD-associated variants CFH Y402H and ARMS2 A69S. Other genes, such as those related to the angiogenesis and coagulation pathways, have also been examined.

The first AMD pharmacogenetic study involved a small series of 27 English patients treated with PDT and genotyped for CFH Y402H. Following treatment, patients with CFH CC lost a median of 12 letters of visual acuity (VA) \((P = 0.038\) compared to CFH TT), while patients with CFH CT lost a median of 3.5 letters \((P = 0.087)\). This study suggested that patients with two CFH Y402H risk alleles fared worse with PDT than those with one risk allele. However, the analysis was limited by having only two treated patients with the CFH Y402H TT genotype, making it difficult to draw conclusions [55].

A subsequent study examined a series of 69 US patients treated with PDT and genotyped for CFH Y402H [56]. Adjusting for lesion type, lesion size, and pretreatment VA, the mean VA after PDT in this study was significantly worse \((P < 0.05)\), as well as for the subgroup of patients with predominantly classic CNV \((P = 0.04)\), but not for patients with occult CNV \((P = 0.22)\). This suggests that the association between PDT outcome and CFH genotype in this study was driven by those patients with predominantly classic lesions. The authors examined ARMS2 A69S genotypes as well and found no statistically significant differences among treatment outcomes with respect to genotype.

Other studies investigating PDT and CFH Y402H have shown no associations between this polymorphism and treatment outcome. A series of 88 Finnish patients treated with PDT was evaluated for an association with the CFH Y402H SNP [57]. This study used a binary responder/nonresponder outcome classification. Patients were considered to be PDT responders if the treating physician deemed the neovascular lesion to be dry without leakage on fluorescein angiography at least 12 weeks after the last treatment. PDT nonresponders were patients whose lesions did not meet this criterion. The investigators found no statistically significant differences among CFH Y402H genotypes with respect to PDT response or the median number of treatments required.
A study including 131 Israeli patients who were treated with PDT and genotyped for the CFH Y402H polymorphism used posttreatment VA as the outcome measure. In this series, there were no statistically significant differences in treatment outcomes by CFH Y402H genotype, with respect to initial VA, post-PDT VA, or number of PDT sessions required [58]. The same group subsequently published a series of 143 patients treated with PDT and reported that genotypes at both ARMS2 A69S and HTRA1 (rs11200638) were not associated with treatment outcomes, in terms of final VA or number of PDT sessions [59].

In a series of 273 Australian patients treated with PDT and genotyped for CFH Y402H, participants were divided into responders and nonresponders based on posttreatment VA. Positive responders were those patients who at the final visit had either an improved or unchanged VA or those who lost fewer than 3 lines of vision (provided their final VA was better than or equal to 20/200). Negative responders were those with a final VA of worse than 20/200 or those who lost 3 or more lines of VA. In this study, there were no statistically significant differences in treatment outcomes with respect to the CFH Y402H genotype. Nine polymorphisms in CRP were also investigated in this study, and two of the nine (rs2808635 GG and rs876538 AA) were significantly correlated with more favorable response to PDT \( P = 0.048 \) and \( P = 0.048, \) resp. [60].

A series of 110 Japanese patients treated with PDT was screened for multiple polymorphisms in CFH, HTRA1, VEGF, and PEDF. The HTRA1 rs11200638 GG genotype was associated with significantly improved visual acuity outcomes and significantly less risk of recurrent disease following treatment \( P = 0.029 \). The combination of two CFH genotypes (rs1410996 and rs2274700) was associated with a statistically significant reduction in the time interval until disease recurrence following PDT \( (P = 0.0085) \). In this study, there was no association between PDT response and CFH SNPs rs1061170 (Y402H) and rs800292, 3 VEGF SNPs (rs699947, rs1570360, and rs2010963), or four PEDF SNPs (rs12150053, rs12948385, rs9913583, and rs1136287) [61].

A series of 86 Finnish patients treated with PDT was examined in the context of three VEGF polymorphisms using a binary responder/nonresponder classification. As in this group’s earlier study, patients were considered PDT responders if the lesion was deemed to be dry at least 12 weeks after the last treatment and PDT nonresponders failed to meet this criterion. Two VEGF polymorphisms (rs699947 and rs2146323) showed a statistically significant relationship to treatment, while one (rs3025033) did not. Regarding the rs699947 genotype, the C allele was associated with a significantly higher percentage of nonresponders \( (P = 0.0003) \). For the rs2146323 genotype, the C allele was again linked to a higher percentage of PDT nonresponders \( (P = 0.0036) \) [62].

Ninety patients treated with PDT for classic CNV were screened for polymorphisms in various genes affecting coagulation, including factor V G1691A, prothrombin G20210A, factor XIII-A G185T, MTHFR C677T, methionine synthase A2756G, and methionine synthase reductase A66G. Patients were classified using a binary responders/nonresponders classification. Responders were significantly associated with the prothrombin G20210A and MTHFR 677T polymorphisms. Nonresponders were significantly associated with the factor XIII-A 185T polymorphism [63]. The same group subsequently reported 84 patients treated with PDT for

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Genes</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT</td>
<td>CFH</td>
<td>CFH CC associated with worse visual outcomes [55]</td>
</tr>
<tr>
<td>PDT</td>
<td>CFH and ARMS2</td>
<td>CFH TT associated with worse visual outcomes, especially in predominantly classic CNV; no association with ARMS2 [56]</td>
</tr>
<tr>
<td>PDT</td>
<td>CFH</td>
<td>No association with PDT responders versus nonresponders [57]</td>
</tr>
<tr>
<td>PDT</td>
<td>CFH</td>
<td>No association with visual acuity outcomes [58]</td>
</tr>
<tr>
<td>PDT</td>
<td>ARMS2 and HTRA1</td>
<td>No association with visual acuity outcomes or number of PDT sessions with either gene [59]</td>
</tr>
<tr>
<td>PDT</td>
<td>CFH and CRP</td>
<td>No effect with CFH; 2 of 9 CRP polymorphisms associated with more favorable response to treatment [60]</td>
</tr>
<tr>
<td>PDT</td>
<td>CFH, HTRA1, VEGF, and PEDF</td>
<td>HTRA1 GG associated with more favorable treatment outcomes; combination of 2 CFH genotypes associated with reduced time interval until disease recurrence; no association with other genes [61]</td>
</tr>
<tr>
<td>PDT</td>
<td>VEGF</td>
<td>2 polymorphisms associated with response to treatment [62] In classic CNV, prothrombin and MTHFR associated with PDT responders; factor XIII-A associated with PDT nonresponders; factor V, methionine synthase; methionine synthase reductase not associated with PDT response [63]</td>
</tr>
<tr>
<td>PDT</td>
<td>Multiple</td>
<td>In occult CNV, combination of factor V and prothrombin associated with PDT responders; factor XIII-A associated with PDT nonresponders; MTHFR, methionine synthase; methionine synthase reductase not associated with PDT response [64]</td>
</tr>
</tbody>
</table>

CNV: choroidal neovascularization, PDT: photodynamic therapy.
occult CNV that were screened for the same six coagulation factor polymorphisms. In this study, nonresponders were significantly associated with the factor XIII-A G185T mutation, and responders were significantly associated with the combination of factor V 1691A and prothrombin 20210A [64]. Of note, the MTHFR 677T polymorphism that correlated with improved outcomes in patients with classic CNV did not correlate with improved outcomes in patients with occult CNV [72].

### 5. Pharmacogenetics of Anti-VEGF Agents

A recent group of studies has reported relationships between genetic variation and response to treatment for exudative AMD with anti-VEGF agents (Table 3). At this time, all of these reports involve bevacizumab, ranibizumab, or both.

The first study to investigate the association between genetic variants and anti-VEGF treatment for AMD was a retrospective series of 86 US patients treated with bevacizumab monotherapy. Patients were treated every six weeks until the CNV was no longer active and genotyped for the cizumab monotherapy. Patients were treated every six weeks.

Table 3: Pharmacogenetics of antivascular endothelial growth factor therapy.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Genes</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>CFH and ARMS2</td>
<td>CFH CC associated with worse visual outcomes; no association with ARMS2 [65]</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>CFH</td>
<td>CFH CC associated with worse visual outcomes [66]</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>CFH</td>
<td>CFH CC associated with more injections performed [67]</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>CFH and ARMS2</td>
<td>ARMS2 TT associated with worse visual outcomes; CFH CC associated with relatively worse visual outcomes [68]</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>Multiple</td>
<td>CFH CC associated with poor treatment response; combination heterozygotes at CFH and FZD4 associated with more favorable outcomes; no association with CFB, HTRA1, ARMS2, VEGFA, KDR, and LRP5 [69]</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>CFH, HTRA1, and VEGF</td>
<td>CFH TC associated with better visual outcomes; no association with number of injections with any gene [70]</td>
</tr>
<tr>
<td>Bevacizumab and/or ranibizumab</td>
<td>APOE</td>
<td>APOE ε4 associated with better treatment outcomes [71]</td>
</tr>
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</table>

In an analysis of 243 eyes treated with ranibizumab monotherapy and screened for genotypes at CFH, CFB, HTRA1, ARMS2, VEGFA, KDR, LRP5, and FZD4, there was a statistically significant difference in treatment response with respect to CFH Y402H. In this study, two responder groups were evaluated: poor responders (≤25th percentile) and good responders (≥75th percentile). The authors reported that 38% of poor responders were associated with CFH CC, while only 15% of good responders were associated with CFH CC. Individual polymorphisms in the other genes were not significantly associated with treatment outcomes, but patients who were heterozygous at both CFH and FZD4 had significantly more favorable results; this genotype combination was identified in 36% of good responders versus 13% of poor responders [69].

A more recent series of 104 patients treated with ranibizumab monotherapy was screened for genotypes at CFH,
HTRA1, and VEGF. There were no significant relationships between any genotype and the number of reinjections within the first 6 months. There were nonsignificant trends towards better visual acuity outcomes with certain genotypes in all 3 loci studied. The percentage of patients with a posttreatment increase in VA greater 5 letters was significantly greater among patients with the CFH TC genotype than those with the CFH TT genotype (P = 0.04), but there was no difference between the CFH CC and CFH TT genotypes [70].

Finally, a series of 172 patients treated with ranibizumab, bevacizumab, or a combination of the two agents was studied for polymorphisms in APOE. The primary endpoint was two-line improvement in visual acuity. The APOE ε4 allele was associated with significantly improved treatment outcomes, as compared with the APOE ε2 allele at 3-month followup (P = 0.02), but not at 12 months (P = 0.06) [71].

6. Pharmacogenetics of Corticosteroids

A series of 52 patients treated with IVTA for a variety of indications, including AMD, was evaluated for a relationship between IOP elevation and 6 polymorphisms in GR (ER22/23EK, N363S, Bcll, N766N, and polymorphisms with introns 3 and 4) (Table 1). There were no statistically significant associations between any individual polymorphism, or by haplotype analysis, with IOP elevation following treatment with IVTA [54].

7. Summary

Several pilot pharmacogenetic studies have reported some evidence of genotype-phenotype interactions with respect to treatment outcomes using AREDS vitamins, PDT, ranibizumab, and bevacizumab. At this point, the data are conflicting and no definite conclusions may be drawn. The results may be inconsistent because of underlying differences in baseline genetic characteristics, differences in underlying CNV lesion characteristics (classic versus occult, chronicity, etc.), differences in study endpoints (visual acuity, anatomic response, number of retreatments required, etc.) statistical analysis (use of continuous outcome versus dichotomizing these variables), or other factors.

At this time, pharmacogenetics remains a research tool rather than an option for daily clinical use. Nevertheless, there appears to be a relationship between CFH, ARMS2, and perhaps other genes with respect to treatment outcomes. As we continue to collect data from clinical trials, these relationships may become more apparent.

Acknowledgments

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References


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