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Review

Genetics and Age-Related Macular Degeneration: A Practical Review for Clinicians

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Abstract

Age-related macular degeneration (AMD) is a multifactorial genetic disease, with at least 52 identifiable associated gene variants at 34 loci, including variants in *complement factor H* (*CFH*) and *age-related maculopathy susceptibility 2/high-temperature requirement A serine peptidase-1* (*ARMS2/HTRA1*). Genetic factors account for up to 70% of disease variability. However, population-based genetic risk scores are generally more helpful for clinical trial design and stratification of risk groups than for individual patient counseling. There is some evidence of pharmacogenetic influences on various treatment modalities used in AMD patients, including Age-Related Eye Disease Study (AREDS) supplements, photodynamic therapy (PDT), and anti-vascular endothelial growth factor (anti-VEGF) agents. However, there is currently no convincing evidence that genetic information plays a role in routine clinical care.

Keywords: age-related macular degeneration; Age-Related Eye Disease Study; geographic atrophy; neovascular AMD; pharmacogenetics

1. Introduction

Age-related macular degeneration (AMD) is a complex multifactorial disease culminating in progressive and potentially irreversible loss of central vision in the elderly. The pathogenesis of AMD is influenced by both modifiable (dietary choices, smoking) and non-modifiable (age, genetic variants) factors [1–9].

AMD can be divided into non-neovascular (non-exudative) and neovascular (exudative) forms, which coexist in the same eye. Intermediate non-neovascular AMD is characterized by drusen and pigment abnormalities. Advanced non-neovascular AMD is characterized by geographic atrophy, which may involve the foveal center. Neovascular AMD is characterized by choroidal neovascularization.

At present, patients with intermediate or advanced AMD are offered nutritional supplements, usually using the Age-Related Eye Disease Study 2 (AREDS 2) formula [10,11]. Patients with neovascular (exudative) AMD are generally treated with intravitreal injections of an anti-vascular endothelial growth factor (anti-VEGF) agent [12]. However, some patients are still treated with photodynamic therapy with intravenous verteporfin under certain circumstances [13]. Patients with geographic atrophy were traditionally observed, although two intravitreal complement inhibitors have recently achieved FDA approval in the US: Pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Astellas Pharmaceuticals) [14]. Notably, there is evidence of a pharmacogenetic effect on many of these interventions [15,16].

2. AMD Genetics

AMD is a complex, polygenic disease with genetic polymorphisms accounting for up to 70% of the disease variability [17]. Unlike a monogenic (Mendelian) disease, AMD heritability is not controlled by a single mutation that can be identified from a pedigree analysis and observed in a family line [18,19]. AMD-related polygenic patterns require population-based analysis and may vary between different populations [17,20–23].

Genes involving at least 25 different biological functions have been reported as being associated with AMD, of which the complement pathways have been studied most intensively [24]. The International AMD Genomics Consortium (IAMDGC) is a multinational collaboration of 33 centers and has provided much relevant data.

The IAMDGC conducted a genome-wide association study (GWAS) of 16,144 AMD patients and 17,832 controls. The investigators reported 52 independently associated variants across 34 loci associated with AMD [17]. Indeed, the most common loci confirmed in multiple studies are *complement factor H* (*CFH*) and *age-related maculopathy susceptibility 2/high-temperature requirement A serine peptidase-1* (*ARMS2/HTRA1*); the latter two variants are strongly associated by linkage disequilibrium [17, 24–27]. Other genes involving the complement cascade, lipid metabolism, extracellular matrix, and immune function have also been associated with AMD [1,17]. Interestingly, most discovered variants are associated with all known AMD stages [1,17,24]. However, a series of 196

patients with geographic atrophy were classified into three distinct subgroups largely by genetic risk scores [28].

GWAS can identify genetic variants associated with specific disease states, and the transcriptome (which includes all RNA transcripts) may provide complementary information. A transcriptome-wide association study (TWAS) can identify associations between gene expression levels and disease states [29]. The IAMDGC also conducted a transcriptome-wide association study (TWAS) of 16,144 AMD patients and 17,832 controls and reported 106 genes significantly associated with AMD variants in at least one tissue, including 28 genes in tibial nerve tissue, 28 genes in subcutaneous adipose tissue, and 26 genes in lung tissue [30].

3. Pharmacogenetics

3.1 Anti-VEGF

Most patients with active neovascular AMD are offered treatment with intravitreal anti-VEGF agents, such as bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), brolucizumab (Beovu, Novartis), and faricimab (Vabysmo, Genentech).

There is substantial interpatient variability in the treatment response, and individual patients appear to respond better to different anti-VEGF agents, which suggests a pharmacogenetic effect [31,32]. Various series have reported statistically significant associations in treatment outcomes (including anatomic factors and visual acuity improvement) with variants at *CFH*, *ARMS2/HTRA1*, and other genes following treatment with bevacizumab, ranibizumab, and aflibercept [31–35]. To our knowledge, no pharmacogenetic studies have currently been published for brolucizumab or faricimab. However, two large, multicenter randomized clinical trials could not replicate these findings [36,37].

A 2022 meta-analysis of 33 case–control series concluded that variants at *CFH*, *ARMS2/HTRA1*, and *olfactory receptor family 52 subfamily B member 4* (*OR52B4*) were significantly associated with the clinical response to anti-VEGF agents [38]. Transcriptome analysis of peripheral blood mononuclear cells from 59 patients treated with ranibizumab demonstrated that the ranibizumab response could be predicted before treatment [39]. However, a 2022 comprehensive review of 41 observational series, 7 meta-analyses, and 5 GWAS reported no consistent patterns among the findings [40].

Table 1 (Ref. [31–45]) demonstrates the variable findings reported in the selected recent series.

3.2 Photodynamic Therapy

Photodynamic therapy (PDT) with verteporfin (Visudyne, Bausch, and Lomb) has been supplanted by anti-VEGF therapy but is occasionally used in the treatment of individual patients [46–49]. Currently, PDT may be offered in combination with anti-VEGF [50,51] or to "rescue" poor responders [13,52,53].

Pharmacogenetic effects have also been reported for PDT monotherapy and combination therapy. Common variants at *CFH* were reported not to be associated with PDT outcomes [54,55], whereas variants at the *vascular endothelial growth factor* (*VEGF*) and *C-reactive protein* (*CRP*) were reported to be associated with improved outcomes after PDT [55,56]. Variants at *ARMS2/HTRA1* have been reported to have no significant association [57] or less favorable outcomes [58] after PDT. Variants in *methylenetetrahydrofolate reductase* (*MTHFR*) were associated with more PDT sessions [59]. Another series reported no associations between *CFH* and *ARMS2/HTRA1* variants and the combination therapy using anti-VEGF and PDT [53].

3.3 Nutritional Supplementation

Large, multicenter, prospective randomized clinical trials have reported the effectiveness of using AREDS and AREDS 2 supplements in reducing AMD progression to geographic atrophy and neovascular disease [10,11]. The AREDS investigators collected genetic data from some study participants, although this information was not included in the original studies.

A retrospective analysis of 876 patients from AREDS reported that more favorable outcomes were associated with no risk alleles at *CFH* than with two risk alleles at *CFH* [60]. Three subsequent retrospective subgroup analyses of patients from AREDS reported significant associations between clinical outcomes and risk alleles at *CFH* and *ARMS2*. Based on these results, these investigators recommended using genotype-directed nutritional supplementation for routine clinical care [61–63].

In response, the AREDS investigators tried replicating this reported association between *CFH*, *ARMS2*, and AREDS supplementation. They studied a "residual cohort" of 526 study participants from AREDS who were not included in the previous pharmacogenetic studies. The AREDS investigators reported that they could not replicate the findings, concluding that no significant associations existed [64,65]. Additional investigators independently reviewed the AREDS data and concluded that no significant genetic associations existed [66]. Subsequently, the AREDS 2 investigators performed a retrospective analysis of 1684 patients from AREDS 2 (as opposed to AREDS) and reported no significant association between *CFH*, *ARMS2*, and the response to nutritional supplements [67].

More recently, a case-only series of 265 patients with neovascular AMD (not analyzed in AREDS or AREDS 2) using an AREDS formulation also reported an interaction between *CFH*, *ARMS2*, and clinical outcomes [68].

Table 1. Selected recent pharmacogenetic association studies.

Genotype	Anti-VEGF agent	Reported association	Study
ARMS2 rs10490924	ranibizumab	Less favorable visual responses in patients with *ARMS2* A69S	Teper 2010 [41]
ARMS2 rs10490924, *HTRA1* rs1-1200638, *CFH* rs1061170, *C3* rs-2230199	ranibizumab, bevacizumab	No significant associations	Hagstrom 2013 [36] Hagstrom 2015 [37]
VEGF rs1413711, rs302503, rs201063, rs833061, rs699947	bevacizumab	No significant associations	Boltz 2012 [42]
VEGFA rs943080	ranibizumab	Less favorable reponses in patients with T risk alleles	Zhao 2013 [35]
VEGFA rs3025000	ranibizumab, bevacizumab	More favorable responses in patients with T risk alleles	Abedi 2013 [43]
VEGFA rs699947	ranibizumab, bevacizumab	No significant associations in randomized clinical trials	Fauser 2015 [34]
CFH, *ARMS2*, *VEGFA*	ranibizumab	A "clinical prediction rule" generated a total risk score for the response	van Asten 2014 [32]
CFH, *C3*, *ARMS2*, mtDNA	ranibizumab	No significant associations	Chaudhary 2016 [31]
OR52B4 rs4910623	ranibizumab	Less favorable responses associated with rs4910623	Riaz 2016 [33]
ABCA1 rs1883025	ranibizumab, bevacizumab	Less favorable responses associated with T risk alleles	Mockute 2021 [44]
Four mRNA and one miRNA	ranibizumab	A "classification model" was associated with the clinical response	Oca 2021 [39]
CFH rs1061170, *C2* rs2230199, *C3* rs9332739	ranibizumab, bevacizumab	Less favorable responses associated with the *CFH* CC genotype	Kubicka-Trząska 2022 [45]
CFH 1061170, *ARMS2* rs1040904, *HTRA1* rs11200638, *OR52B4* rs323085	ranibizumab, bevacizumab	Treatment responses were associated with nine polymorphisms in four genes	Wang 2022 [38]
30 variants	ranibizumab, aflibercept	No significant associations	Strunz 2022 [40]

Anti-VEGF, anti-vascular endothelial growth factor; *VEGFA*, *vascular endothelial growth factor A*; *OR52B4*, *olfactory receptor family 52 subfamily B member 4*; *CFH*, *complement factor H*; *ARMS2*, *age-related maculopathy susceptibility 2*; *HTRA1*, *high-temperature requirement A serine peptidase-1*; *ABCA1*, *adenosine triphosphate binding cassette subfamily A member 1*.

4. Applying These Results to Clinical Practice

Clinical genetic testing is an important part of emerging personalized medicine [69]. The ability to better risk-stratify patients can improve outcomes by better allocating scarce resources to the patients most in need or by selecting the most effective treatment from alternatives [1,26]. Up to 70% of the clinical variability in AMD can be explained by genetic variants [1,17,20], meaning this disease may be amenable to personalized medical approaches.

Population-based genetic risk scores are powerful tools for the risk stratification of populations and for designing clinical trials. However, they are less helpful in the clinical management of an individual patient, whereby a patient with a favorable genetic profile may, nevertheless, develop an advanced disease and vice versa. Many series have reported various statistically significant genetic associations with PDT, anti-VEGF injections, and nutritional supplementation, although the results are inconsistent and frequently conflicting. There may be many reasons, including baseline population differences, small sample sizes, heterogeneous treatment protocols, and differences in outcome measures. It has been suggested that a sample size of at least 15,000 patients would be necessary to definitively identify genetic associations with responses to anti-VEGF therapy [40].

There is a commercially available genetic test in the US and Canada that specifically offers genetic-based recommendations. Currently, the authors do not use this testing in their clinical practices as repeated attempts to replicate these findings from multiple investigators have failed.

From a personalized medicine perspective, in the opinion of the authors, genetic analysis of patients with AMD does not play a role in current clinical management. There is no convincing evidence that using genetic infor-

mation improves clinical outcomes, meaning there is currently no indication to perform genetic sequencing on patients with AMD.

5. Conclusions

AMD, a complex disease, is affected by both genetic and non-genetic (environmental) factors. Pharmacogenetic associations show great promise as a research tool, although at this time, genetic testing for AMD is not indicated in routine clinical care.

Abbreviations

AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; *ARMS2/HTRA1*, *age-related maculopathy Susceptibility 2/high-temperature requirement-A serine-peptidase-1*; *CFH*, *complement factor H*; *CRP*, *C-reactive protein*; GWAS, genome-wide association study; *OR52B4*, *olfactory receptor family 52 subfamily B member 4*; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor; TWAS, transcriptome-wide association study.

Author Contributions

JN: research and draft the manuscript. MAB: design, review and approve the manuscript. SGS: design, research, draft the manuscript, review, and approve. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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