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REVIEW

Genetics and age-related macular degeneration: a practical review for the clinician

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Abstract: Age-related macular degeneration is a complex disease, with both genetic and environmental risk factors interacting in unknown ways. Currently, 52 gene variants within 34 loci have been significantly associated with age-related macular degeneration. Two well-studied major genes are *complement factor H* (*CFH*) and *age-related maculopathy susceptibility 2* (*ARMS2*). There exist several commercially available tests that are proposed to stratify patients into high-risk and low-risk groups, as well as predict response to nutritional supplementation. However, at present, the bulk of the available peer-reviewed evidence suggests that genetic testing is more useful as a research tool than for clinical management of patients.

Keywords: age-related macular degeneration, *age-related maculopathy susceptibility 2*, *ARMS2*, *complement factor H*, *CFH*, pharmacogenetics, vascular endothelial growth factor

Introduction

Age-related macular degeneration (AMD), in both neovascular and non-neovascular forms, is a leading cause of irreversible visual loss throughout the developed world. AMD is a complex disease with both genetic and environmental risk factors. Recent advances in genetic testing have led to greatly increased understanding of these genotype–phenotype associations. This manuscript is intended to provide a concise review of the genetic basis of AMD for the practicing clinician, including a brief overview of genetic testing, risk variants associated with AMD, and risk variants associated with response to various AMD therapies (pharmacogenetics).

Genetic testing

Many diseases have one or more genetic risk factors. It is important to distinguish monogenic (single gene or Mendelian) diseases from complex genetic diseases.

Generally speaking, monogenic diseases are relatively infrequent and, by definition, caused by a single gene. The patients will often have a familial history consistent with an autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance pattern, which may be ascertained by pedigree analysis. Frequently, multiple different single gene defects lead to a similar clinical phenotype. Examples of retinal monogenic diseases include Best vitelliform macular dystrophy (generally autosomal dominant), Leber congenital amaurosis (generally autosomal recessive), juvenile retinoschisis (generally X-linked), retinitis pigmentosa (multiple inheritance patterns), and others. Typically, individuals carrying the relevant mutation are highly likely to develop the associated disease. Therefore, there is a rationale to screen for the mutation in asymptomatic individuals, and these diseases are, at least in theory, relatively more amenable to gene therapies than are complex genetic diseases.[1]

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In contrast, complex genetic diseases are more common and associated with multiple genetic and environmental risk factors. These patients will typically not have a familial history that suggests a specific inheritance pattern, and pedigree analysis is generally not helpful in this situation. Examples of retinal complex genetic diseases include diabetic retinopathy[2] and AMD. Certain genetic variants, known as risk alleles or polymorphisms (as opposed to mutations), are associated with increased risk of disease, as opposed to protective alleles which are associated with decreased risk of disease. Risk alleles are not necessarily "abnormal" in the same sense as mutations, and they are typically present in at least 1% of the population. Individuals carrying one or more risk alleles may not develop the disease, while individuals lacking risk alleles may develop the disease. Therefore, from a clinical perspective, knowledge of a patient's genotype is less valuable for a complex genetic disease. Subsequently, there is no rationale to screen for these risk alleles in asymptomatic (or even affected) individuals, and these diseases are relatively less amenable to gene therapies.

Another important consideration is the fact that many published genetic association studies might be misleading. Individual reports may yield statistically significant associations, but these findings may be due to factors other than a true genetic association. These may include differences in baseline demographics of the study population, differences in clinical ascertainment, selection bias, and other factors. Therefore, it is important to validate the findings, preferably with at least one additional population.

The American Academy of Ophthalmology created a task force on genetic testing and published recommendations in 2012,[3] which were updated in 2014.[4] These recommendations included the following: offering genetic testing to patients suspected of having a monogenic (Mendelian) disease; providing genetic counseling (or referring to a genetic counselor); avoiding direct-to-consumer genetic testing; and avoiding routine testing of complex genetic diseases such as AMD.

AMD genetics

AMD is not a monogenic disease caused by a single gene defect. Rather, it is a complex disease with both genetic and environmental risk factors. Reported environmental risk factors include age, smoking, dietary nutrients, exogenous estrogen use, and others.[5] The genetic component of AMD has been estimated at 45% to 70%.[6] As of this writing, 34 genetic loci, encompassing 52 gene variants, have been associated with AMD; it has been estimated that these 52 variants collectively account for about half of the heritability of the disease.[7] These genes and genomic regions may be divided into high-effect, low-effect, and unknown variants.[8]

The two most widely studied and important loci, due to their large effect sizes and relatively high frequencies in the population, are *complement factor H* (*CFH*)[9–12] and *age-related maculopathy susceptibility 2* (*ARMS2*).[13] *ARMS2*, previously termed *LOC387715*, is in very strong linkage disequilibrium with another gene, *high temperature requirement A serine peptidase 1* (*HTRA1*),[14] and the effects of these two loci are statistically indistinguishable. It is uncertain whether *ARMS2* or *HTRA1* is more clinically relevant.

Significant gene–environment interactions may also occur. For example, smoking is correlated with AMD, and this association has been reported to be stronger in smokers with certain variants in *nitric oxide synthase 2A* (*NOS2A*).[15] Alternatively, hormone replacement therapy is negatively correlated with AMD in women, and this negative association has been reported to be stronger in women with certain *ARMS2* variants.[16] These results are interesting from a research perspective, but they have not been validated by other series.

It is uncertain which patients with early AMD will progress to advanced disease, including neovascular AMD and central geographic atrophy. Most risk alleles are associated with both neovascular AMD and geographic atrophy, but it has been reported recently that a variant near *MMP9* (*matrix metallopeptidase 9*) was associated only with neovascular AMD; this is the first neovascular-specific allele identified.[7]

AMD genetic testing in the clinic

Because AMD is a complex genetic disease, knowledge of any one risk allele is of limited or no value to an individual patient. In contrast, a genetic risk score, calculated from known genetic and environmental risk factors, would seem to be clinically useful in advising patients about individual risk.[17] The accuracy of this risk score is very important because a falsely low score may give a patient a false sense of security, while a falsely high score may expose patients to psychological stress, as well as (potentially) unnecessary examinations and perhaps medical interventions.

One measure of the accuracy of a predictive model uses a statistic known as area under the curve (AUC), in which an AUC of 0.5 indicates chance (no accuracy), an AUC of 1 is completely accurate, and an AUC of ≥ 0.75 suggests a useful model.[18] Models based on either clinical or genetic information may meet this definition of usefulness. For example,

some clinical models, with no genetic information, have achieved AUCs of ≥0.76.[19,20] Alternatively, some genetic risk models, with no clinical data, have achieved AUCs of ≥0.81.[21,22] It is reasonable to suspect that models combining clinical and genetic data may yield even more accurate information, but this is not always the case. Various combined models have reported AUCs of ≥0.75.[23–29]

There are currently at least three commercially available genetic AMD tests. In the US, Macula Risk PGx (ArcticDx, Toronto, ON, Canada) is ordered by a care provider. EasyDNA (Kent, UK) and Asper Biotech (Tartu, Estonia) offer direct-to-consumer genetic testing. RetnaGene (Sequenom, San Diego, CA, USA) is no longer available. 23andMe (Mountain View, CA, USA), another direct-to-consumer product, does not specifically list AMD among its offered "carrier status reports" on its website.

Macula Risk PGx analyzes 15 variants across 12 loci, as well as age, body mass index, smoking history, and educational level. The test analyzes these results and stratifies the patient into one of five "Macula Risk" categories, which are associated with varying degrees of risk of progression to advanced AMD. This laboratory also offers a second test, "Vita Risk", which uses variants at *CFH* and *ARMS2* to predict response to nutritional therapy (discussed later).

A task force from the Centers for Disease Control and Prevention and the National Institutes for Health created the ACCE model to evaluate the utility of various genetic tests.[30] The model considers four variables. Analytic validity measures the accuracy (sensitivity and specificity) with which the genetic information is detected. Clinical validity measures the extent to which the genetic test predicts the clinical phenotype. Clinical utility measures the ability of the test to improve clinical outcomes. And the last variable encompasses the Ethical, legal, and social implications of the test.

Therefore, the ACCE model may be applied to the Macula Risk test. This test is based on a statistical model with a reported AUC of 0.883 for 5-year progression and 0.895 for 10-year progression, which suggests excellent analytic validity and clinical validity.[31] However, one model incorporating only clinical data, with no genetic data, reported a similar AUC of 0.88,[20] which suggests that comparable validity may be achieved without any genetic testing whatsoever.

The clinical utility of the Macula Risk test is less certain. It would seem intuitive that identifying the patients at highest risk of progression to advanced AMD (including neovascular AMD and central geographic atrophy) would be valuable, but putting this information into clinical practice is not straightforward. One might recommend more frequent examinations for higher-risk patients, but there is little or no peer-reviewed evidence to support such a strategy. The utility of genetic testing for predicting response to nutritional supplementation will be discussed later.

The ethical, legal, and social implications of this test may be substantial, especially in terms of the psychosocial stress associated with a potentially incorrect risk assessment. Lower-risk patients may progress to advanced disease while higher-risk patients may not. These implications are intensified if one of the direct-to-consumer tests is requested by a young, asymptomatic patient. For these reasons, the American Academy of Ophthalmology task force specifically advised against testing for complex genetic diseases such as AMD and also advised avoiding direct-to-consumer genetic testing.[4]

AMD pharmacogenetics

AMD is treated primarily with pharmacotherapies. Patients with neovascular AMD are generally treated with anti-vascular endothelial growth factor (VEGF) agents, including ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA), aflibercept (Eylea, Regeneron, Tarrytown, NY, USA), and bevacizumab (Avastin, Genentech).[32] In addition, patients with at least intermediate AMD are typically offered nutritional supplementation as per the Age-Related Eye Disease Study (AREDS)[33] and AREDS 2[34] trials.

There is increasing evidence of genetic influences on response to ophthalmic medications. Such outcomes have been reported with betaxolol,[35] latanoprost,[36] intraocular corticosteroids,[37] and other medications.[38] Similarly, many small series have reported statistically significant associations between various anti-VEGF agents and variants in *CFH*, *ARMS2*, and other genes.[39] However, these findings have not been validated and major randomized clinical trials have not reported any statistically significant associations.

For example, the Comparison of AMD Treatments Trials (CATT) compared patients with neovascular AMD treated with bevacizumab or ranibizumab and reported no significant correlations between various anatomic and visual outcomes and variants in *CFH*, *ARMS2*, *HTRA1*, and *complement factor 3* (*C3*);[40] *endothelial PAS domain-containing protein 1* (*EPAS1*);[41] and *VEGF A* (*VEGFA*) and *VEGF receptor 2* (*VEGFR2*).[42] Similarly, the Inhibit VEGF in Patients with Age-Related Choroidal Neovascularization (IVAN) Study also compared patients with neovascular AMD treated with bevacizumab or ranibizumab and reported no

significant correlations between total retinal thickness on optical coherence tomography and variants in *CFH*, *HTRA1/ARMS2*, *EPAS1*, and *frizzled class receptor 4* (*FZD4*).[43] Using pooled data from CATT and IVAN, no significant correlation was reported between mean change in visual acuity and *VEGFR2*.[44]

There may be more evidence supporting a pharmacogenetic relationship with AREDS nutritional supplementation to reduce risks of progression to advanced AMD (including neovascular AMD and central geographic atrophy).[45] AREDS categorized AMD patients using a 1–4 scale in which categories 1 and 2 had mild disease; category 3 had at least one large (≥125 μm) druse, extensive intermediate (63–124 μm) drusen, and/or noncentral geographic atrophy; and category 4 had central geographic atrophy, neovascular AMD, and/or visual loss resulting from AMD in one eye. AREDS randomized patients to receive one of four treatments: antioxidants alone (beta-carotene, vitamin C, and vitamin E), zinc alone (zinc plus copper), antioxidants plus zinc, and neither (placebo). In patients with category 3 or 4 AMD, treatment with antioxidants plus zinc – which subsequently became the AREDS formulation – was associated with an approximate 25% decrease in progression rates at 5 years. AREDS collected genetic information from some of the participants but did not incorporate these results into their findings.[33]

A retrospective subgroup analysis of 876 patients with category 3 or 4 disease from the AREDS trial subsequently compared outcomes of patients stratified by genotype at *CFH* and *ARMS2*. The investigators reported that all patients in this subgroup benefited from AREDS supplementation but patients with no risk alleles at *CFH* experienced significantly more favorable outcomes than did patients with two risk alleles at *CFH*. There was no association with *ARMS2*. Despite the statistically significant association with *CFH*, the investigators did not recommend a change in treatment (because all patients experienced some benefit) and called for additional studies to corroborate the genetic findings.[46]

Awh et al performed another retrospective subgroup analysis of 995 patients with category 3 disease from the same AREDS trial. They compared genotypes at *CFH* and *ARMS2* with outcomes stratified by the four treatment categories (antioxidants, zinc, both, and neither). The investigators reported multiple significant genotype–phenotype correlations in which patients with certain genotypes experienced more favorable outcomes with some nutritional supplements than with others. They reported that 49% of patients analyzed had genotypes in which antioxidants plus zinc (the AREDS formulation) was associated with worse outcomes than one of the other treatment categories. The investigators concluded that a pharmacogenetic approach, in which patients were assigned to nutritional supplementation based on genotypes at *CFH* and *ARMS2*, might lead to more favorable outcomes.[47]

In response to this publication, the AREDS investigators performed an "unplanned retrospective analysis" of a subgroup of 1,237 patients with category 3 or 4 disease from the same AREDS trial. In contrast to Awh et al, the AREDS investigators[48] reported no significant associations between progression rates stratified by nutritional supplementation and genotypes at *CFH* and *ARMS2*.

Awh et al then published yet another retrospective subgroup analysis of 989 patients with category 3 or 4 disease from the original AREDS trial. They again reported a complex relationship between *CFH*, *ARMS2*, and outcomes stratified by nutritional supplementation. They concluded that "most" patients would benefit from either no supplementation at all or a supplementation other than the AREDS formulation (antioxidants plus zinc). They noted the lack of an available replication sample with which to validate their findings, but they reiterated their recommendation that patients be offered genotype-directed nutritional supplementation.[49]

The AREDS investigators then attempted to validate the findings in the two reports by Awh et al. Because Awh et al analyzed only a subset of the patients in the original AREDS trial, the AREDS investigators hypothesized that the remaining (nonanalyzed) patients could be similarly studied, which could represent a replication sample. The investigators then identified 526 patients from the original AREDS trial not previously analyzed by Awh et al and reported that the findings were not replicated. The investigators specifically reported that, among the 526 patients analyzed, the AREDS formulation (antioxidants plus zinc) was the most beneficial nutritional supplement for all genetic subtypes studied.[50]

To date, there has not yet been a prospective clinical trial published that specifically studied genotype–phenotype relationships with respect to nutritional supplementation. There have been five separate retrospective subgroup analyses of the initial AREDS study data which have led to conflicting conclusions. One study reported a significant difference in progression rates among patients with risk variants at *CFH* but did not recommend any change in standard clinical treatment.[46] Two studies by Awh et al[47,49] reported a complex relationship between risk variants at *CFH*, *ARMS2* and

clinical outcomes and recommended using genotype-directed nutritional therapy in order to improve overall outcomes. Two studies by the AREDS investigators[48,50] reported no significant differences, including an attempt to replicate the findings of Awh et al.

How should the practicing clinician interpret these conflicting studies? Certain general principles seem appropriate. First, a randomized clinical trial which was designed to answer a specific question offers a higher level of evidence than does a retrospective subgroup analysis from the same trial that attempts to answer a separate question (in this case, whether genetic information can be used to guide nutritional therapy).[51]

Second, as discussed earlier, genetic association studies may be misleading. Inadvertent selection bias may lead to statistically significant correlations that are not "true" in a clinical sense; this is especially likely as the number of individual comparisons increases. For example, many small series have reported statistically significant pharmacogenetic associations with respect to anti-VEGF therapy, but large clinical trials specifically attempting to uncover these relationships have found no such associations. Therefore, it is generally advisable to replicate the findings with a second (unrelated) study population before recommending large-scale changes to clinical practices.[52]

Third, because AMD is a complex disease, with both genetic and environmental risk factors that interact in unknown ways, it is perhaps not surprising that analyzing risk variants at only two loci (*CFH* and *ARMS2*) yields limited information. There exist many patients with risk variants at both loci who do not develop AMD, just as there exist many patients with no risk variants at either locus who do develop AMD. Therefore, testing only *ARMS2* and *CFH* may yield misleading results that are not useful clinically.[53]

Conclusion

In patients with monogenic diseases, knowledge of an individual patient's genotype is important to confirm the diagnosis and to offer prognostic information. In contrast, AMD is a complex disease with both genetic and environmental risk factors. There is an increasing body of literature which gives insight into risk variants at *CFH*, *ARMS2*, and many other loci, but at present there is not convincing evidence that genetic testing is beneficial in the routine clinical care of patients with AMD. As additional clinical trials are performed, perhaps the situation will change. But for now, genetic testing is more useful as a research strategy than in day-to-day clinical management.

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Disclosure

The authors report no conflicts of interest in this work.

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