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REVIEW

Update on the role of genetics in the onset of age-related macular degeneration

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Peter James Francis
Michael L Klein

Macular Degeneration Center, Casey Eye Institute, Oregon Health and Science University, Portland, OR, USA

Abstract: Age-related macular degeneration (AMD), akin to other common age-related diseases, has a complex pathogenesis and arises from the interplay of genes, environmental factors, and personal characteristics. The past decade has seen very significant strides towards identification of those precise genetic variants associated with disease. That genes encoding proteins of the (alternative) complement pathway (*CFH*, *C2*, *CFB*, *C3*, *CFI*) are major players in etiology came as a surprise to many but has already lead to the development of therapies entering human clinical trials. Other genes replicated in many populations *ARMS2*, *APOE*, variants near *TIMP3*, and genes involved in lipid metabolism have also been implicated in disease pathogenesis. The genes discovered to date can be estimated to account for approximately 50% of the genetic variance of AMD and have been discovered by candidate gene approaches, pathway analysis, and latterly genome-wide association studies. Next generation sequencing modalities and meta-analysis techniques are being employed with the aim of identifying the remaining rarer but, perhaps, individually more significant sequence variations, linked to disease status. Complementary studies have also begun to utilize this genetic information to develop clinically useful algorithms to predict AMD risk and evaluate pharmacogenetics. In this article, contemporary commentary is provided on rapidly progressing efforts to elucidate the genetic pathogenesis of AMD as the field stands at the end of the first decade of the 21st century.

Keywords: genes, complex disease, susceptibility, AMD

Introduction

Individuals who develop age-related macular degeneration (AMD) lose central vision due to involvement of the macula, the central region of the retina specialized to distinguish fine detail, thus permitting activities such as reading, recognizing faces, and driving. Although several retinal layers are affected, vision is primarily lost when photoreceptors die. The term age-related maculopathy (ARM) describes the spectrum of age-related macular changes, from the early presence of a few small drusen (subretinal lipid and protein-containing deposits which are the hallmark of the condition) to the most advanced stages with severe anatomic changes accompanied by vision loss.[1,2] Patients with larger and more numerous drusen, often with advanced or visually significant ARM, are referred to as having AMD.[3] Two advanced forms of the disease are recognized: "dry" or atrophic AMD (geographic atrophy), in which atrophy of the retinal pigment epithelium (RPE) results in untreatable progressive visual loss; and "wet" or neovascular AMD, characterized by the intraretinal invasion of vessels from the choroid, which usually bleed and form dense macular scars.

Correspondence: Peter James Francis
Macular Degeneration Center,
Casey Eye Institute, Oregon Health and Science University, 3375 SW Terwilliger Blvd, Portland, OR 97239, USA
Tel +1 503 418 1627
Fax +1 503 494 7233
Email francisp@ohsu.edu

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One-and-three-quarter million individuals in the United States have the advanced, visually disabling form of AMD. More than seven million additional individuals have earlier retinal changes, placing them at high risk of developing advanced AMD. In those older than 75 years, the prevalence of advanced disease is approximately 8%, and 30% will develop degenerative macular changes consistent with earlier forms of the disease.[4] With the expected increase in the number of older individuals in the population, it is predicted that the prevalence of AMD will increase by more than 50% by the year 2020, substantially increasing the health burden from AMD.[5]

Neovascular AMD is the cause of most cases of legal blindness. Symptoms may progress rapidly over days to weeks, with the major complaints being reduced acuity and distortion. Clinical examination typically reveals the presence of subretinal fluid and hemorrhage. Intra- and subretinal edema and hemorrhage may also be accompaniments.[6,7] As the disease progresses, retinal gliosis may develop, together with permanent visual loss. Neovascularization is best delineated on fluorescein angiography where several patterns are well recognized. The mainstay of clinical evaluation has recently become optical coherence tomography, which has enabled very sensitive detection of retinal and subretinal fluid and therefore guides the need for treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents.[8] Geographic atrophy is characterized by enlarging area(s) of outer retinal atrophy (retinal pigment epithelium and photoreceptors) in the macular region that typically and inexorably expands to affect the fovea.

Extensive epidemiologic and genetic analyses have lead to the conclusion that AMD, like many other chronic age-related diseases, results from the interplay of multiple environmental and genetic factors, which in combination account for development of the phenotype. The condition is strongly age-related, and tobacco smoking is the most consistent and modifiable significant risk factor.[9–11] Other environmental risk factors that have been reported include cardiovascular disease,[12–14] hypertension,[15,16] high body mass index,[17] and low education level.[18]

Genetic susceptibility and AMD

It is now beyond question that genes play a significant etiological role in AMD.[19,20] Studies to identify genetic AMD-susceptibility variants have utilized all available techniques such as genome-wide linkage approaches (twins, sib pairs, and families)[21–27] and case-control association studies. A table of replicated AMD-susceptibility genes is shown in Table 1. For the most part, studies have been limited to the study of the phenotypic extremes; that is, advanced cases or those with no signs of the condition, and case-control populations of extreme phenotypes. This is because it is reasonably achievable to ascertain these phenotypes. There are a few clinical caveats. Firstly, while it is straightforward to identify advanced AMD, often atrophy and neovascular disease coexist either in the same eye or in the fellow eye, and how to group these individuals is potentially problematic. Furthermore, it is less routine to rule out the presence of neovascular AMD in an eye with apparent geographic atrophy. Since the presence of small drusen is almost universal in older individuals, it is somewhat arbitrary how few need to be present for an eye to remain a control.

Table 1 Replicated AMD-susceptibility genes

Gene	Effect of minor allele on odds ratio of having AMD
CFH	↑
ARMS2	↑
C2	↓
C3	↑
CFI	↑
ABCA1	↑
LIPC	↑
CETP	↑
LPL	↑
Near TIMP3	↑

Abbreviation: AMD, age-related macular degeneration.

Intermediate stages of AMD are more difficult to phenotype and require quantification of such endophenotypes such as drusen (size, number, distribution, area) and macular pigment epithelial changes (hypo-/hyper-, area) which are challenging and less well appreciated from the perspective of disease staging. As such, very limited information is currently available regarding the genetic architecture of intermediate AMD.

Early studies

Early studies concentrated on genome-wide linkage and familial association analyses (twins, sib pairs, and families).[21–23] The first genetic locus for AMD was localized in a single large pedigree to chromosome 1q.[28] Later, a co-segregating variant in *HMCN-1* (*hemicentin-1*) was identified.[29] *HMCN-1* lies in close proximity to the *CFH* (*complement factor H*) gene, discussed below. Meta-analysis of a number of linkage studies[24] consistently identified this same locus and several other genomic regions which were later shown to harbor specific genetic variants. Others remain the subject of further investigation.[25–27]

Complement genes

The first well established specific genetic variant to be associated with advanced AMD was the single nucleotide polymorphism (SNP) rs1061170 (T1277C; Y402H) in the *CFH* gene.[30–32] This finding has been replicated by numerous studies.[33] Additional analyses of the *RCA* locus on chromosome 1q in which the gene resides have concluded that haplotypes encompassing both *CFH*[34,35] and neighboring genes,[36] acting independently or in concert with the Y402H change, confer increased risk of drusen formation and advanced AMD.[33,37] Subsequent analyses of the complement pathway identified SNPs in other complement components: complement factors *C2*, *CFB*,[38,39] *C3*,[40,41] and *CFI*.[42] CFH is a regulator of complement activation, dysfunction of which has been linked to retinal pathology.[43]

The challenges of 10q26

Early genome-wide linkage studies consistently identified an AMD susceptibility locus on chromosome 10q26.[24,25] A combination of genotyping and direct sequencing of this region initially identified two SNPs, 6 kb apart, in high linkage disequilibrium in many Caucasian populations,[44] that are strongly associated with advanced AMD, as follows.

- The rs10490924 (A69S) variant lies within the putative gene, *LOC387715*, now named *ARMS2* (*age-related maculopathy susceptibility 2*).[45,46] *ARMS2* has no known function, and the predicted protein shows little homology with other proteins. *ARMS2* is only present in higher primates, and mRNA transcripts can be detected in the retina. Whether the protein is translated is still debated. Immunohistochemical analyses have provided conflicting evidence localizing protein within the mitochondrion[47] in the inner segment of the photoreceptor;[48] the cytoplasm, among other locations. Most recently, an indel in *ARMS2* has been reported that appears to affect translation of the protein and has been postulated to be the functional variant at the 10q26 locus.[48]
- The rs11200638 SNP resides in the promoter of the gene, *HTRA1*,[49,50] a serine protease found in the retina (among other tissues). Preliminary, functional analyses suggest that the polymorphism at this position alters expression levels of the gene.[49]

The era of genome-wide SNP-association studies (GWAS)

Modern advances in genotyping technology have facilitated the high-throughput analysis of hundreds of thousands of single-nucleotide polymorphisms on a single chip. In 2010, a consortium of researchers published the results of two independent GWASs with subsequent replication of positive findings. These studies identified several new genes associated with advanced AMD status.[51,52] Of interest, this study implicated genes associated with lipid metabolism, specifically the HDL pathway, *ABCA1*, *LIPC*, *CETP*, and *LPL*. Other replicated findings included significantly associated SNPs near the gene encoding *TIMP3* (tissue inhibitor of metalloproteinase 3), which is involved in remodeling of the extracellular matrix in the retina.

Other genes

Associations in the genes APOE (apolipoprotein E),[53–55] ABCA4 (ATP-binding cassette A4),[56,57] CX3CR1 (chemokine 3 receptor 1),[58,59] PON1,[60] TLR4 (toll-like receptor 4),[61] ERCC6,[62] ELOVL4,[63,64] VLDLR (very low density lipoprotein receptor),[65] fibulin-5,[66] hemicentin-1,[29] TLR3 (toll-like receptor 3),[67] C1q (complement factor C1q),[68] VEGF (vascular endothelial growth factor),[65,69,70] SERPING1,[71,72] and LRP6[65] have been reported in single populations.

Pharmacogenetics in AMD

The identification of common genetic variants that contribute significantly to the etiology of AMD has garnered interest in evaluating whether these same SNPs and other candidate genes may play a role in treatment response (pharmacogenetics).

Pharmacogenetics attempts to define the genetic variants that determine variable response to medication. The ultimate goal is to identify those who respond best and avoid adverse reactions. Garrod first recognized a familial or genetic tendency to variability in drug response[73] and hypothesized that drugs were metabolized by specific pathways of genes in which defects would result in differences in drug concentrations and therefore drug effect. A large number of studies have now defined pharmacogenetic interactions in many biomedical fields. These include therapies for neurological and psychiatric disorders,[74–76] asthma,[77] cardiovascular disease,[78] and cancer.[79,80]

Initial studies in AMD have focused on three different treatments: Age-Related Eye Disease Study (AREDS) supplementation, photodynamic therapy (PDT), and anti-VEGF therapy. In all instances, studies to date have been limited to retrospective analyses.

Anti-VEGF agents

In one retrospective study, 86 patients being treated with bevacizumab (Avastin™) alone were evaluated for associations between treatment response and common

polymorphisms in the genes *CFH* and *ARMS2*. Patients homozygous for both CFH risk alleles (CC) had worse visual outcomes than those with the CFH TC and TT genotypes.[81] In a similar retrospective analysis, but involving 156 patients who were receiving ranibizumab, the same authors were able to replicate this finding.[82] These studies were well conducted; however, the associations do not necessarily imply causality and there may have been additional confounders.

AREDS supplements

The AREDS was an 11-center National Institutes of Health-funded study initiated in 1992 with 4757 participants. It included an 8-year randomized control trial which established that a combination of zinc and antioxidants (beta-carotene, vitamin C, and vitamin E) produced a 25% reduction in development of advanced AMD and a 19% reduction in severe vision loss in individuals determined to be at high risk of developing the advanced forms of the disease.[6] Conversely, 22% of participants receiving antioxidants and zinc had a 15-letter decrease in visual acuity despite treatment. Use of these oral supplements is now current standard of practice in the United States. Indeed, they remain the only therapy for early, intermediate,[6] and dry AMD.[83]

A recent evaluation of the AREDS cohort found evidence of an interaction between the *CFH* genotype and treatment with antioxidants plus zinc when compared with placebo. This interaction appears to have arisen because 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%).

These results may imply that the strong genetic predisposition to AMD conferred by the CC genotype limits the benefits available from zinc and antioxidants (beta-carotene, vitamin C, and vitamin E).[84] In this pharmacogenetics study, the authors evaluated whether known AMD-susceptibility genotypes in those who at entry into the study had early to intermediate AMD and progressed to advanced disease were associated with treatment assignment. Previously, these same genes had been reported to be independently associated with progression to advanced AMD.[85,86] There is good biological plausibility to support a possible role for *CFH*. Evidence supports the assertion that CFH protein dysfunction results in excessive inflammation and tissue damage of the type involved in the pathogenesis of AMD.[9,20] Inflammation is known to intensify oxidative stress,[21] and since AREDS supplements are thought to have an antioxidant effect,[22–25] it seems reasonable to assume that *CFH* polymorphisms could play a role in treatment response.[13,14]

PDT

PDT was until recently the most widely used therapy for neovascular AMD and still retains a role for individuals in whom anti-VEGF agents are contraindicated.[87] PDT to the macula induces thrombosis of neovascular vessels (choroidal neovascularization) which have been photosensitized by the administration of verteporfin.[88] Efficacy was originally established in a series of randomized control trials including the TAP (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy), VIP (Visudyne in Photodynamic Therapy), and Visudyne in Minimally Classic Choroidal Neovascularization studies.[87] Considerable variability in response is observed with PDT and may vary by ethnicity.[89] In an attempt to identify whether genetic influences are involved, a set of variants in genes associated with thrombosis were retrospectively evaluated in two studies (84 and 90 subjects). Patients were divided into those that were PDT "responders" and those that were "nonresponders" (3-month follow-up). Patients were genotyped for factor V G1691A, prothrombin G20210A, factor XIII-A G185T, methylenetetrahydrofolate reductase C677T, methionine synthase A2756G, and methionine synthase reductase A66G. "Nonresponse" was more frequent in those with the hyperfibrinolytic G185T gene polymorphism of factor XIII-A, and response was associated with those with the thrombophilic factor V 1691A and prothrombin 20210A alleles.[89–91]

As this article is being written, several other prospective pharmacogenetic studies are nearing completion. Cumulatively, these should provide further significant insights into those variants involved with treatment response in AMD.

Predicting the risk of developing advanced AMD

The idea of employing a risk assessment algorithm to identify individuals at risk of developing AMD is attractive. The fact that drusen, the hallmark of the condition, appear prior to the development of vision loss offers an unusually useful clinical feature that might be combined with genetic and environmental risk factors to give an accurate risk assessment. Several such models have been proposed. Seddon et al described a model derived from the AREDS study population that included all these factors using the AREDS clinical AMD grading scale.[92] In the model, points are assigned for the risk factors in their model to determine an individual's risk score. Zanke et al described a model that gives a lifetime risk estimate based on genetics and environmental factors,[93] and recently Chen et al proposed a model that examined risk of bilateral involvement.[94] There is no conclusive evidence that

genetic variants assist in predicting progression of disease once advanced AMD is established. One study found no association of progression of geographic atrophy with variants in the *CFH*, *C3*, and *ARMS2* genes.[95] A second study found no association of progression with variants in *CFH*, *C2*, *C3*, and *CFI*, but did note a nominal association with *ARMS2*.[96]

Concluding remarks

AMD is a major health burden and one that is rapidly growing as the population of the Western world ages, en masse. Although the introduction of anti-VEGF agents has revolutionized outcomes for those with the less common neovascular form of AMD, there is limitation to the effectiveness of these regimens. There is currently neither effective treatment for geographic atrophy nor for earlier stages of disease. Dissecting the genetic etiology of the condition holds substantial promise for the identification of new avenues for therapeutic development. It is likely that conventional genome-wide and candidate gene approaches may have reached their limit to resolve new variants. Genome-wide strategies are not themselves redundant but will be superseded by next-generation technology such as whole Exmore and full genome sequencing.[97] Furthermore, the analysis of individuals with intermediate AMD phenotypes and the use of extended pedigrees with carefully quantified endophenotypes offer the opportunity to investigate less common, rarer, and private mutations, otherwise largely unidentifiable using case-control populations.

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Disclosure

The authors report no conflicts of interest in this work.

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