Genetic Basis of Age-related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is the main cause of vision loss and impairment in the aging population in developed countries. It is clinically and genetically a complex disease with both environmental and genetic factors affecting the outcome of the disease. Other than the wet type of AMD, there is no treatment for the other forms of AMD. It is estimated that the number of AMD patients will double in the next decade, which will have a significant financial impact on the health system and will compete for health dollars. Understanding the role of genetics in the development of AMD is paramount to help with diagnosis and future treatment. Over the past few years, we have studied the genetics of AMD and reported modest to significant association between AMD and several genes including CFH, ARMS2, TLR4 and ApoE. Our recent genome-wide association studies confirmed these AMD susceptibility loci in addition to other genes in the complement system (C2, C3, CFB and CFI). Recent studies identified new loci near TIMP3 and HDL influencing susceptibility to AMD.

Keywords

Age-related macular degeneration, genes, macular degeneration, susceptibility loci

Disclosure: This research was supported by grants from the NEI/NIH (R01 EY016862), NEI/NIH Core Center for Vision Research (P30 EY07003), Foundation Fighting Blindness, and the Elmer and Sylvia Sramek Foundation.

Received: February 10, 2011 **Accepted:** March 14, 2011 **Citation:** *US Ophthalmic Review*, 2011;4(2):119–21 *DOI: 10.17925/USOR.2011.04.02.119*

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Literature Review

Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in the elderly population in the developed world. This major health problem is expected to worsen with the projected increase in numbers of the aging population. A full understanding of the pathobiology of the disease process is still elusive, and is compounded by the heterogeneous nature and complexity of the disease.[1,2] Family history and linkage studies point toward a multigenic basis for AMD,[3–5] including genetic factors which affect aging and mitochondrial contributions to aging.[6–13] There are known environmental factors, such as diet, phototoxicity, smoking, drinking white wine (as opposed to red wine), and inflammatory insults to the retina, during the lifetime of patients that will contribute to an increased or decreased risk of developing disease.[14–17] Currently, the contribution of inflammation and complement components to the pathology of AMD is generating new interest. Several reports have discussed the role of the immune system in AMD.[18–24] Recently, a number of association studies identified sequence variants in the complement factor H (CFH) gene to be significantly associated with AMD.[25–30] Other complement components and factors were shown to increase the risk of AMD.[31–36]

This article focuses on the genetic basis of macular degeneration and will discuss briefly the results of our reported studies, current studies, and plans for future studies. Our primary aim has been to identify the genes that cause or are intimately associated with the pathophysiology of AMD, which in turn identifies the pathways and processes underlying the development of AMD. Eventually, these studies will help develop drugs designed specifically to treat AMD, or to significantly delay the progress of AMD in the aging population.

Early genetic investigations into AMD worked to understand the familial contribution to disease and focused on twin studies and familial aggregation studies. Twin studies have demonstrated complete concordance (100 %) for both members of monozygotic twin pairs being affected with AMD and usually being affected with the same stage of disease.[37–39] This can be compared with the data looking at dizygotic twin pairs, which showed a lower concordance (42–50 %) for being affected with AMD.[37,39] Similarly, familial aggregation studies have shown a higher prevalence of AMD among first-degree relatives of affected probands as compared with first-degree relatives of control probands.[40,41] Results from these early studies demonstrated the useful role of family history in studying AMD, and paved the way for future genetic linkage and association studies.

Early association studies focused on genes that had been previously identified in diseases manifesting with similar retinal phenotypes to AMD (i.e. macular dystrophies). Association studies looking at the EFEMP1,[42] ELOVL4,[43] RDS,[44] TIMP3,[45] and VMD2[46,47] genes have yet to reveal strong associations in AMD patients. Although some early studies indicated an association of AMD with mutations in ABCA4,[48,49] further studies did not demonstrate an association with this gene.[50–52]

Identification of susceptibility loci for AMD requires the application of classical genetic studies and more advanced genome-wide association studies (GWAS). The aims of these studies are to confirm the role of genetics in AMD and to identify genes that might cause AMD or be associated with the development of AMD. Several classical linkage studies were carried out using panels of markers spanning the entire chromosomes against AMD patients (families and sib-pairs).[53–57] GWAS, using high-density single nucleotide polymorphism (SNP) chips, were used to precisely localize AMD-associated genes.[28,58] In this article we will focus on the major loci identified by these studies.

Linkage Studies

We performed an association linkage analysis with high-density markers (5 cM) on 412 affected relative pairs, primarily affected with geographic atrophy and/or neovascularization.[53] Our analysis confirmed earlier linkage studies data[54,55,59] and identified other possible areas of interest for study. The first locus on chromosome 1q31 turned out to include CFH, a gene involved in regulating the function of C3 in the alternative complement pathway. Meta-analysis of various reported linkage studies identified several AMD loci.[4] Furthermore, a recent review from our laboratory on the status of AMD and current genetic susceptibility studies had compiled the linkage loci and localized them to regions on different chromosomes.[60] The results of the various linkage studies reflected the complexity and heterogeneity of AMD. However, there were two clear AMD association loci that were identified in several linkage analysis studies, located at 1q31 and 10q26.[53–55]

Sequence Variants in Candidate Genes and their Association with Age-related Macular Degeneration

Candidate genes for associated studies were selected based on knowledge of gene functions and/or information obtained from linkage studies. These genes were sequenced using our Michigan AMD cohort (over 850 cases and controls) to identify any sequence variants. Statistical analysis was done to compare the probabilities of the genotypes and alleles frequencies in both AMD cases and controls. Apolipoprotein E alleles were studied to determine if any of the alleles would be associated with AMD. The ApoE4 allele was shown to be protective from AMD, and was present in controls at a significantly higher frequency than in the AMD cases;[61] also, our results confirmed findings which are in agreement with the findings of previous studies, with one difference, that our sample size was larger.[62,63] The toll-like receptor 4 (TLR4) gene was investigated for a possible association with AMD due to the implication that inflammation and the complement system pathways are involved in AMD.[21–23,64] This gene was selected because it is localized to 9q32-33, another locus found by our AMD association linkage studies. Furthermore, it was an attractive candidate as it is considered a pro-inflammatory gene.[65,66] The D299G TLR4 sequence variant was shown to be significantly associated with AMD.[67] Recently, we repeated an association study between AMD and SNPs in the toll-like receptor 3 (TLR3) and toll-like receptor 7 (TLR7) genes. In spite of our not finding an association between our AMD cases and these genes (analyzing 610 AMD patients and 324 controls), the SNPs in those genes were reported to be associated with AMD in another cohort.[68] A recent analysis identified a protective role of a variant in the TLR3 gene against geographic atrophy.[69] The TLR association remains open to further study.

1q32 and Complement Factor H

The identification of CFH on 1q32, as the first major AMD association locus, resulted from a genome-wide association study. The Y402H SNP was hailed as a significant finding because it related to increased risk of AMD and to the function of CFH. This change was predicted to alter the function of CFH and pointed to the role of complement components in the development of AMD.[28] Several studies reported similar findings, with increased risk of AMD with the Y402H allele.[25–27] We repeated the association study with CFH Y402H, using our large cohort of AMD cases and controls, and reported similar findings as the previous studies and showed that this risk allele is highly associated with AMD.[30] We extended our CFH study identifying other SNPs that had a stronger association with AMD than the Y402H SNP. By examining 84 SNPs in the region of CFH, we found that several haplotypes that do not include Y402H had a stronger association with AMD than Y402H alone.[29]

The 10q26 Locus and Age-related Macular Degeneration

Several linkage studies have confirmed 10q26 to be a major AMD association locus.[57,70,71] The region includes three nearby genes (PLEKHA1, LOC387715 and HTRA1). Reports showed that one SNP (rs11200638) in the promoter region of HTRA1 is highly associated with AMD.[58,72] However, our work and the work of others has shown that the rs10490924 SNP, in the hypothetical gene LOC387715 (now known as ARMS2), has a stronger association with AMD than rs11200638.[73–77] ARMS2 is of interest because it is only present in higher primates that have maculae (humans and chimpanzees). We reported that the ARMS2 gene protein is expressed and localized to the mitochondria of transfected cell lines.[74] A recent study confirmed our findings by showing that the LOC387715 protein is expressed and localized to the mitochondria in photoreceptors.[73] This study also identified a deletion/insertion in the 3' end of ARMS2 that accelerates the decay of the mRNA. This may be one of the reasons why the protein and mRNA are not being expressed or detected in the mitochondria of AMD-affected individuals.[73]

Recent Studies

The genetics of AMD are complex and far more difficult to investigate compared with typical monogenic diseases. Identifying the various genetic loci that contribute to the AMD disease process will eventually be able to put the big picture together so we can start to understand the genetic pathways active in individual patients which are influencing them to develop AMD. To address this, we were involved in a multicenter study with over 3,000 AMD cases and controls in an attempt to find new loci as part of a new GWAS consortium using the Illumina Human370 bead chips and the Illumina Infinium II assay protocol. Our GWAS data were published recently,[78] where we confirmed the earlier findings for the two major susceptibility loci (CFH and ARMS2), in addition to the other loci for C2/CFB, C3, and CFI. This comprehensive study identified additional susceptibility loci with genetic variants near the regions of TIMP3 and HDL-associated loci. When this study looked at all susceptibility loci, 329/331 (99 %) cases were identified and 85 % of them had advanced AMD. Future work is needed to verify the role of these genes in the diagnosis, development, progression, and treatment of AMD. ■

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