

Genetic Basis of Age-related Macular Degeneration

The Haplotype Map has elucidated the complex and polygenic basis of AMD.

BY JACLYN L. KOVACH, MD

Age-related macular degeneration (AMD) is the major cause of irreversible blindness in older adults in the western hemisphere.¹ Approximately 30% of Americans aged 75 years and older have AMD,² and, by 2020 it is estimated that 3 million Americans will be affected by advanced AMD.³ The etiology of AMD involves a complex interaction of inflammatory, oxidative, degenerative, and genetic components. The developing field of human genomics has fostered significant advancements in our knowledge of the genetics of AMD.

THE HAPLOTYPE MAP PROJECT

Before the completion of the International Haplotype Map Project in 2005, familial aggregation studies were the basis for our conception of AMD heritability. These studies demonstrated that first-degree relatives of affected patients have a fourfold increased risk of developing the condition, and that monozygotic twins are known to have a high level of concordance for AMD compared with dizygotic twins.⁴⁻⁷ Underlying genes of heritable retinal dystrophies, including TIMP3, EFEMP1, ABCA4, RDS, ELVOL4, and VMD2,⁸ have been investigated as possible candidate genes associated with AMD, but to date a pathogenic role has been proven only for TIMP3⁹ and ABCA4.⁸

The completion of the International Haplotype Map Project enabled the identification of millions of single nucleotide polymorphisms (SNP), normal variations in gene structure that may protect against or predispose to various diseases. Genome-wide association studies have identified several susceptibility loci associated with increased AMD risk.

SUSCEPTIBILITY LOCI

Complement factor H (CFH), complement factor B (CFB)/complement component 2 (C2), LOC387715/ARMS2 and HTRA1 are believed to be responsible for the majority of heritable AMD risk.¹⁰⁻¹² The first major susceptibility gene discovered for AMD was complement factor H SNP Y402H (rs1061170) on chromosome 1q32. This particular polymorphism, which could be responsible for at least 50% of AMD risk, causes abnormal complement activation and host cell destruction secondary to ineffective binding of CFH to Bruch membrane. CFH Y402H promotes the development and progression of all stages of AMD and can act synergistically with smoking history to increase one's risk of wet AMD.¹³⁻¹⁴

Various SNPs in the complement factor I (CFI),¹⁵ complement factor B/complement component 2 (CFB/C2),¹¹ and complement component 3 (C3) genes promote complement activation and increase AMD risk. Complement component 3, the convergence point of the complement pathways, promotes the formation of the membrane attack complex (MAC) and consequential cell lysis. Nine SNPs in the C3 gene are associated with AMD, with SNP R102G specifically related to wet AMD.¹⁶

The consequence of uncontrolled complement activation affects every step in AMD pathogenesis, including leukocyte accumulation, reactive oxygen species and drusen formation, retinal pigment epithelial (RPE) cell damage (MAC-induced cell lysis), and elevation of vascular endothelial growth factor (VEGF) levels with resultant choroidal neovascularization (CNV).¹⁵

The second major susceptibility locus identified for AMD was LOC387715/ARMS2 A69S and HTRA1, which

occupy several kilobases on a segment of chromosome 10q26. ARMS2 mediates oxidative stress, and HTRA1 is a serine protease present in drusen. Homozygosity for this high-risk polymorphism confers increased risk for AMD progression.¹²

AMD susceptibility is associated with polymorphisms in the LIPC, CETP, LPL, ABCA1 and APOE genes, which play a role in cholesterol metabolism.⁹ Genetic variants with weak or questionable AMD associations include HMCN1, VEGF, TLR3, TLR4, and Serping1.^{17,18}

CONCLUSION

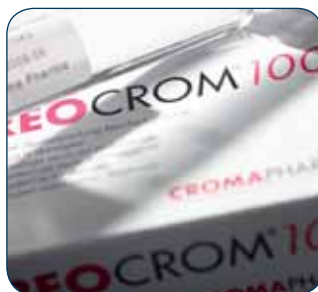
During the past few years our level of understanding of the complex and polygenic basis of AMD has improved dramatically. This knowledge has provided the foundation for genetic testing and the potential for gene-guided treatment and gene therapy. ■

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