A
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 esti-
mated that 3 million Americans will be affected by
advanced AMD.\(^3\) The etiology of AMD involves a com-
plex interaction of inflammatory, oxidative, degenera-
tive, 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 stud-
ies 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 di-
zygotic twins.\(^4-7\) Underlying genes of heritable retinal dys-
trophies, 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 TIMP3\(^9\) 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 suscep-
tibility gene discovered for AMD was complement factor H
SNP Y402H (rs1061170) on chromosome 1q32. This partic-
ular 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),\(^15\) com-
plement factor B/complement component 2 (CFB/C2),\(^11\)
and complement component 3 (C3) genes promote com-
plement 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 activa-
tion 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 vascu-
lar 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

Genetic Basis of Age-related Macular Degeneration

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

BY JACLYN L. KOVACH, MD
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.1

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