

Genetics of Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment and blindness in developed countries, with an estimated 10 million people (1 in 27) affected in the U.S. During normal aging, small deposits called drusen accumulate under the retina. AMD arises when an abnormal number of intermediate or large drusen are deposited in the macula (the central region of the retina). The drusen, along with other changes in the macula such as cell death and abnormal blood vessel growth, cause loss of vision.¹ There is no cure for AMS; treatments are based on early detection and methods to preserve vision.

AMD is a complex disease resulting from the interplay of multiple risk factors,² both genetic and environmental.¹ The strongest environmental risk factor is cigarette smoking, which can more than double the risk of developing AMD. Other environmental factors under study are diet, race, and cardiovascular risks.²

Recent studies have revealed a clearer picture of the genetic contribution to AMD, showing that genes regulating the inflammatory response are most involved. It is now thought that 3 out of 4 cases of AMD result from variations in one or more genes.³ The Y402H variant of the gene that encodes complement factor H (CFH) significantly increases risk for the development of AMD. CFH is an inhibitor of the complement pathway; activation of the complement pathway enhances inflammation. The Y402H variant is thought to decrease the inhibitory function of CHF, leading to inflammation.⁴ Those carrying two copies of this variant have an approximately 48% chance of developing AMD, compared to 22% for noncarriers.² A variant in complement component C3 is also thought to increase risk for AMD.^{1,2}

A variation in a gene located on chromosome 10, *LOC387715*, also seems to increase risk for AMD, conferring a more than 7-fold increase in risk for homozygous individuals.² While the function of *LOC387715* is unknown, it has been demonstrated to be localized to the mitochondria, leading to speculation that the variation in *LOC387715* causes mitochondrial dysfunction that results in oxidative damage to the retina. Interestingly, cigarette smoking, the most common environmental risk factor for AMD, is also thought to cause oxidative stress.

Complicating the genetic control of AMD are variations that seem to confer protection. Complement factor B (CFB) and complement component 2 (CC2) play key roles in the activation of the alternative and classical complement pathways, respectively.^{1,2} Variations in the coding sequences of these genes are protective for AMD, likely because the variations inhibit the complement pathways, resulting in decreased inflammation.

Determination of risk for developing AMD is based on which genetic variants, both risk-increasing and protective, an individual patient carries, combined with environmental risk factors such as smoking that each patient experiences. There are genetic tests that will reveal whether a patient carries variations in some of the AMD risk genes, however it is still too early to know whether test results can impact treatment decisions.

1. Haines JL, Spencer KM, Pericak-Vance MA. (2007) Bringing the genetics of macular degeneration into focus. *PNAS* 104, 16725-16726.

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3. Medical News Today. Genetic Discovery Explains 74% of Cases of Macular Degeneration. Published 3/13/2006.

4. Despriet DDG, Klaver CCW, Wittman JCM, Bergen AAB, Kardys I, et al. (2006) Complement Factor H Polymorphism, Complement Activators, and Risk of Age-Related Macular Degeneration. *JAMA* 296, 300-309.