

Update on Factor H and Genetic Predisposition to AMD: How Geneticists Understand the Disease

There have been major advances in determining what causes AMD—with the main focus on complement factor H.

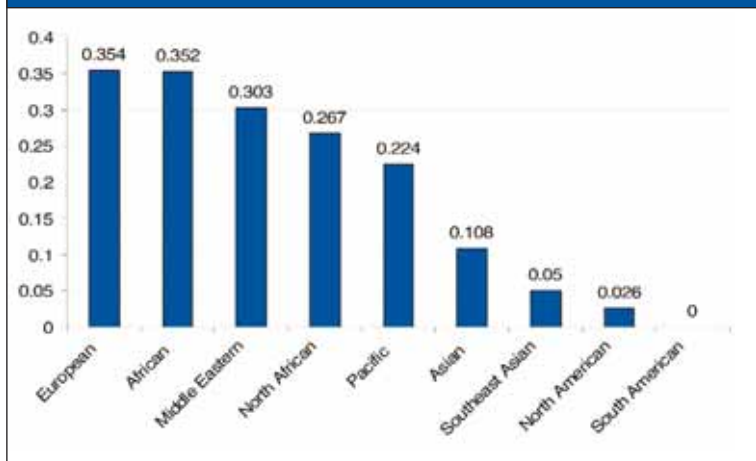
REVIEWED BY RANDO ALLIKMETS, PhD

We study the genetic origins of age-related macular degeneration (AMD) because we have to know the exact genetic cause of a disease to treat the source, said Rando Allikmets, PhD, speaking in Las Vegas at Retina 2006: Emerging New Concepts, held in conjunction with the American Academy of Ophthalmology annual meeting.¹ Today, all treatment options are for the late stages of the disease when it is usually too late to improve vision. “Ultimately, we want to treat the cause and not the symptoms,” he said. Dr. Allikmets is the William and Donna Acquavella Associate Professor of Ophthalmic Science in the Departments of Ophthalmology and Pathology & Cell Biology at Columbia University.

There have been great advances in determining what causes AMD, he said, with the main focus on complement factor H (CFH) haplotypes. In early studies Dr. Allikmets’ team indicated that there are several variables in CFH that change one’s risk for AMD.² These studies have been extended recently by several groups.^{3,4}

It has been noted that across ethnic populations the variation in genes also varies in numbers (Table 1), Dr. Allikmets said. “So to analyze the major AMD-associated CFH allele Y402H variant, we looked across all populations. This variant is very high in Europeans and Africans, and then its frequency goes down—it is much less fre-

TABLE 1. FREQUENCY OF THE CFH Y402H VARIANT IN POPULATIONS



quent in Asians and almost nonexistent in Native American populations.”

POPULATION ANALYSES

Population analyses of Y402H have led researchers to make some conclusions: The factor H variants are major genetic determinants of AMD in the white population. Many other populations with high incidence of AMD, however, have a lower frequency of 402H. In blacks, who have a frequent occurrence of 402H and similar rates of early AMD as whites, there is much less incidence of late stage AMD.

There could be several reasons for this, Dr. Allikmets

TABLE 2. GENETIC LOCI FOR AMD

CFH locus	CFHR3	CFHR1	Effect
162V IV56 Y402H A473A	delCFHR3/1		
G T C C	+		High risk
G T T T	+		Low risk
A T T T	+		Protective
G C/t T T	del		Protective

C2/BF locus	Effect
E318D Int10 L9H R32Q	
G G T G	Low risk
G T T A	Protective
C G A G	Protective

10q26 locus	Effect
rs10490224 rs11200638	
T A	High risk
G G	

said. “The homozygous deletion protective allele is much more common in black (about 16%) than in white populations (about 5%). So we have to not only look at one variant but the entire gene and how it confers risk or protection.”

CFH haplotypes developed very rapidly in an evolutionary context. The fact that 402H is present at a high frequency in Africa suggests that it has an ancient origin. This brings up the question of why the risk variant was not retained in all populations.

EVOLUTION

“The hypothesis is that the considerable diversity accumulated at CFH locus is due to selection, consistent with an important role for these genes in innate immunity,” Dr. Allikmets said. “Alleles with altered functionality are subject to selection and maintained to protect against different triggers or pathogens. While robust complement activity directed against specific pathogens is desirable, it may lead to a higher risk of inflammation-related disorders with a late onset which are not subject to selection.”

When the analyses of factors H and B are combined, close to three-quarters of all AMD can be explained based on two gene variations.⁵ “Factor B unequivocally proved that the complement cascade is at the beginning of all AMD, and it defines well our next good therapeutic target.”

There is a third AMD locus on 10q26, which contains three genes.⁵⁻⁷ It is not known at this time what gene in what variant causes AMD. Studies have defined a variant that is present in this locus as associated with late-onset AMD, Dr. Allikmets emphasized, as opposed to the vari-

ation in the complement cascade genes, which is associated with all AMD regardless of the stage.

CAN WE PREDICT?

“So what we know right now is that there are three major loci—factor H, factor B, and 10q—and all of them contain multiple risk or protective variants,” Dr. Allikmets said.

Now that we have explained the disease, can we predict it? Current genetic knowledge explains most of AMD, however we can only predict its occurrence in extreme situations, Dr. Allikmets said. We will not have 100% efficiency for predicting the disease any time soon. “But do we need 100%? Probably not at this time; it all depends on what kind of treatment you are suggesting to people. If the treatment is very invasive, only the highest risk group (double homozygotes for CFH and

10q locus) will be treated. If the treatment has few side effects, it can be administered to all patients.”

The current hypothesis of how AMD develops may be simplistically summarized as follows: Triggering of complement response initiates inflammation. If a person has a genetic susceptibility, a local chronic inflammation may persist, resulting in the formation of drusen, the early sign of AMD. Together with other genetic (for example, the variant in 10q locus) and environmental (smoking, diet, etc.) factors, late-stage AMD may develop in some cases. ■

Rando Allikmets, PhD, is the William and Donna Acquavella Associate Professor of Ophthalmic Science in the Departments of Ophthalmology and Pathology & Cell Biology at Columbia University. He may be reached at rla22@columbia.edu; phone: 212-305-8989; or fax: 212-305-7014.

- Allikmets R. Update on factor H and genetic predisposition to AMD. Presented at Retina 2006: Emerging New Concepts, held in conjunction with the American Academy of Ophthalmology annual meeting. Nov. 10-11, 2006. Las Vegas.
- Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2005;102:7227-7232.
- Li M, Atmaca-Sonmez P, Othman M, et al. CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. *Nature Genetics*. 2006;38:1049-1054.
- Maller J, George S, Purcell S, et al. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. *Nature Genetics*. 2006;38:1055-1059.
- Gold B, Merriam JE, Zernant J, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. *Nature Genetics*. 2006; 38:458-462.
- Jakobsdottir J, Conley YP, Weeks DE, et al. Susceptibility genes for age-related maculopathy on chromosome 10q26. *Am J Hum Genet*. 2005;77:389-407.
- Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Hum Mol Genet*. 2005; 14:3227-3236.