

# CFH Polymorphism May Cause More Than Half of All AMD Cases

Complement factor H is involved in early as well as late disease pathogenesis, and it markedly increases the risk of late AMD in the elderly.

REVIEWED BY PAULUS T.V.M. DE JONG, MD, PhD

**T**he complement factor H (CFH) gene Y402H polymorphism appears to account for a substantial proportion of age-related macular degeneration (AMD) in patients similar to those in the Rotterdam Study and may confer particular risk in the presence of environmental and genetic stimulators of the complement cascade, according to new research published in the *Journal of the American Medical Association*.

There is growing evidence that inflammation is an important pathway in AMD, wrote Paulus T.V.M. de Jong, MD, PhD, and colleagues. Other case-control studies have shown an association between the CFH gene, a regulator of complement, and AMD (Figure 1). AMD is the most prevalent cause of irreversible vision loss in elderly patients in the Western world. In addition to recent studies showing that inflammation is an important disease mechanism, it has also long been recognized that hereditary factors play a role in AMD.

## ASSESSED THE ASSOCIATIONS

The investigators assessed the associations between the CFH gene and AMD in the general population and investigated the modifying effect of smoking, serum inflammatory markers and the genetic variation of C-reactive protein (CRP). To achieve this, they used a



Figure 1. A scene as it might be viewed by a person with AMD.

Photo courtesy of National Eye Institute, National Institutes of Health

population-based prospective cohort study of patients aged  $\geq 55$  years who were living in Rotterdam, Netherlands. Patients were enrolled between March 20, 1990 and July 31, 1993 and had three follow-up exams conducted between Sept. 1, 1993 and Dec. 31, 2004. The presence of the CFH Y402H polymorphism was assessed in 5,681 individuals. The researchers also obtained information on smoking, erythrocyte sedimentation rate, CRP serum levels and haplotypes of the CRP gene at baseline.

The study's main measure of outcome was all severity stages of prevalent and incident AMD, grading

according to the international classification and grading system for the condition.

Dr. de Jong and colleagues found a prevalence of 36.2% for the CFH Y402H gene (4,116 of 11,362 alleles). They wrote that at baseline, there were 2,062 people (36.3%) with any type of AMD (prevalent cases) including 78 (1.4%) with late AMD or stage 4 AMD. During a mean follow-up of 8 years, 1,649 (35.5%) of 4,642 participants progressed to a higher stage of AMD (incident cases), including 93 (5.6%) who developed late AMD.

### INCREASE IN ALLELE-DOSE MANNER

Dr. de Jong and his colleagues wrote that the odds ratio (OR) of AMD increased in an allele-dose manner with 2.00 (95% CI, 1.56-2.55) for stage 2 AMD, 4.58 (95% CI, 2.82-7.44) for stage 3 AMD and 11.02 (95% CI, 6.82-11.81) for stage 4 (late, vision-threatening) AMD for homozygous patients.

Cumulative risks calculated by Kaplan-Meier analysis, the authors wrote, were 48.3% for late AMD by age 95 years for homozygotes, 42.6% for heterozygotes, and 21.9% for noncarriers. The population-attributable risk for CFH Y402H was 54.0%. Elevated erythrocyte sedimentation rates further increased the OR to 20.2 (95% CI, 9.5-43.0), elevated serum CRP levels to 27.7 (95% CI, 10.7-72.0) and smoking to 34.0 (95% CI, 13.0-88.6) for homozygotes compared with noncarriers who did not have these determinants, they said.

The CRP haplotypes conferring high levels of CRP significantly increased the effect of CFH Y402H ( $P < .01$ ), Dr. de Jong wrote.

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### IMPORTANT REGULATOR

“Complement factor H is an important regulator of the complement system,” Dr. de Jong said. “Three enzyme cascades exist: the classical complement pathway, initiated by antigen-antibody complexes and surface-bound CRP; the lectin, turned on by mannose groups of microbial carbohydrates; and the alternative complement pathway, activated by surface-bound C3b.” He went on to explain that the pathways converge at the point in which C3 is cleaved into C3a and

### THE ROTTERDAM STUDY

The Rotterdam Study was a prospective population-based cohort study of chronic diseases in the elderly. The eligible population comprised all 10,275 inhabitants of Ommoord, a suburb of Rotterdam, Netherlands, aged  $\geq 55$  years. The participants were invited by mail, contacted by telephone for a home interview and exams at the research center.

Of the eligible population, 78% participated, 58% were female and 98% were white.

The ophthalmic portion of the Rotterdam Study consisted of 9,774 eligible individuals of whom 78% participated.

*Source: Despriet DDG, Klaver CCW, Witteman JCM, et al. Complement Factor H polymorphism, complement activators, and risk of age-related macular degeneration. JAMA. 2006;296:301-309.*

C3b by C3 convertase, which initiates C5 convertase and results in the formation of the membrane attack complex with the terminal components.

“Complement factor H specifically inhibits the alternative complement cascade but also regulates the common pathway. It binds C3b and acts as a cofactor in the proteolysis of C3b by factor I, resulting in an inactive C3b molecule. This prevents the production of C3 convertase in the alternative cascade as well as the production of C5 convertase in the common pathway. CFH interferes with the progression of the entire cascade,” Dr de Jong wrote.

### ENVIRONMENT PLAYS A ROLE, TOO

This inhibitory gene, CFH, is a major risk factor for AMD. The effect of CFH is also significantly influenced by environmental and genetic factors that determine the inflammatory response and activate the complement pathway, the investigators concluded. “Future research on therapeutic modalities that help regulate the terminal complement pathway, thereby sparing host tissue, may provide an approach for preventing sight-threatening AMD in genetically predisposed individuals.” ■

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