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No Clinically Significant Association between *CFH* and *ARMS2* Genotypes and Response to Nutritional Supplements

AREDS Report Number 38

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Objective: To determine whether genotypes at 2 major loci associated with late age-related macular degeneration (AMD), *complement factor H* (*CFH*) and *age-related maculopathy susceptibility 2* (*ARMS2*), influence the relative benefits of Age-Related Eye Disease Study (AREDS) supplements.

Design: Unplanned retrospective evaluation of a prospective, randomized, placebo-controlled clinical trial of vitamins and minerals for the treatment of AMD.

Subjects: AREDS participants (mean age, 69 years) who were at risk of developing late AMD and who were randomized to the 4 arms of AREDS supplement treatment.

Methods: Analyses were performed using the Cox proportional hazards model to predict progression to late AMD (neovascular or central geographic atrophy). Statistical models, adjusted for age, gender, smoking status, and baseline AMD severity, were used to examine the influence of genotypes on the response to therapy with 4 randomly assigned arms of AREDS supplement components: placebo, antioxidants (vitamin C, vitamin E, β-carotene), zinc, or a combination.

Main Outcome Measures: The influence of the genotype on the relative treatment response to the randomized components of the AREDS supplement, measured as progression to late AMD.

Results: Of the 1237 genotyped AREDS participants of white ethnicity, late AMD developed in 385 (31.1%) during the mean follow-up of 6.6 years. As previously demonstrated, *CFH* genotype ($P = 0.005$), *ARMS2* ($P < 0.0001$), and supplement were associated individually with progression to late AMD. An interaction analysis found no evidence that the relative benefits of AREDS supplementation varied by genotype. Analysis of (1) *CFH* rs1061170 and rs1410996 combined with *ARMS2* rs10490924 with the 4 randomly assigned arms of AREDS supplement and (2) analysis of the combination of *CFH* rs412852 and rs3766405 with *ARMS2* c.372_815del443ins54 with the AREDS components resulted in no interaction ($P = 0.06$ and $P = 0.45$, respectively, before multiplicity adjustment).

Conclusions: The AREDS supplements reduced the rate of AMD progression across all genotype groups. Furthermore, the genotypes at the *CFH* and *ARMS2* loci did not statistically significantly alter the benefits of AREDS supplements. Genetic testing remains a valuable research tool, but these analyses suggest it provides no benefits in managing nutritional supplementation for patients at risk of late AMD. *Ophthalmology 2014;121:2173-2180 © 2014 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Age-related macular degeneration (AMD) is the leading cause of blindness in the United States, with nearly 2 million late AMD cases and 8 million intermediate AMD cases estimated in 2004.[1] With increased population longevity, the numbers of individuals affected with AMD are projected to double by 2024.[1] The Age-Related Eye Disease Study (AREDS) followed up persons with intermediate AMD (large drusen or extensive medium drusen) or late AMD in only 1 eye at enrollment and demonstrated that, over 5 years, the AREDS supplements, consisting of antioxidants (vitamin E, vitamin C, and β-carotene) and zinc (plus copper), reduced the risk of development of late AMD, especially neovascular AMD, by 25% (Fig 1A).[2]

Age-related macular degeneration is a complex disease with both heritable and environmental risks. Epidemiologic studies have revealed the exponential increase in prevalence of AMD with age, an increase in risk conferred by smoking, a protective effect of fatty fish and green leafy vegetable

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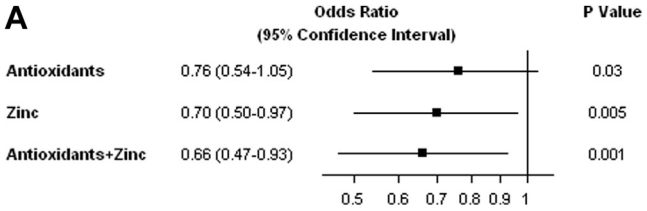

Figure 1. **A**, Graph showing the overall results of the Age-Related Eye Disease Study (AREDS). (Reprinted from: Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001; 119:1417–36.) **B**, Graph showing combined influence of *complement factor H* (*CFH*) rs1061170 and rs1410996 and *age-related maculopathy susceptibility 2* (*ARMS2*) rs10490924 (n = 1237) genotypes on treatment with AREDS supplement components. Model includes age, gender, smoking, baseline age-related macular degeneration (AMD) category, AREDS treatment, *CFH*/*ARMS2*, and the interaction term of AREDS treatment and *CFH*/*ARMS2*. Because of multiple comparisons, Bonferroni correction requires $P<0.001$ to reach statistical significance. *CFH*: 0 = low risk, 1 = medium risk, and 2 = high risk; *ARMS2*: 0 = low risk (GG), 1 = medium risk (GT), and 2 = high risk (TT); and *CFH*/*ARMS2* = *xy*, where *x* = *CFH* risk group and *y* = *ARMS2* risk alleles. **C**, Graph showing combined influence of *CFH* rs412852 and rs3766405 and *ARMS2* (c.372_815del443ins54; n = 1413) genotypes on treatment with AREDS supplement components (antioxidants, zinc, or combination of antioxidant and zinc). Model includes age, gender, smoking, baseline AMD category, AREDS treatment, *CFH*/*ARMS2*, and the interaction term of AREDS treatment and *CFH*/*ARMS2*. Because of multiple comparisons, Bonferroni correction requires $P<0.001$ to reach statistical significance. *CFH*: 0 = low risk, 1 = medium risk, and 2 = high risk; *ARMS2* (815del443ins54): 0 = low risk, 1 = medium risk, and 2 = high risk; *CFH*/*ARMS2* = *xy*, where *x* = *CFH* risk group and *y* = *ARMS2* risk alleles. CI = confidence interval. *Denominator is too small to calculate a hazard ratio.

consumption, and a less consistent association with body mass index and hypertension.[3–9] Genetic studies have identified 19 susceptibility loci that seem to explain more than 50% of the risk of AMD developing.[10] These studies point to biological pathways that may contribute to AMD pathogenesis; these include alternative complement activation, high-density lipoprotein cholesterol transport and metabolism, extracellular matrix integrity and cell adhesion, and angiogenesis.[3]

An important question is whether knowledge of individual risk genotypes could inform the choice of therapeutic strategy among at-risk individuals, as happens now in some areas of medicine. For example, in oncology, information on genetic variants that predict successful responses to therapy (or adverse events) has led to genetically informed treatment strategies.[11,12] Numerous studies have evaluated the association of genetic testing and treatment with anti–vascular endothelial growth factor drugs for neovascular AMD with retrospective analyses.[13–18] These have been studies with varying outcome variables and durations, resulting in no clear consensus about this association. Genetic information has not added to clinical factors such as visual acuity at baseline, lesion size, age, and interval between symptoms and treatment that seem to be important in determining the visual outcomes after treatment.[19]

Five years ago, Klein et al[20] evaluated possible genetic predictors of response to treatment with the AREDS supplement. Included in the analyses were all 867 AREDS participants with intermediate AMD (large drusen or extensive medium drusen in 1 or both eyes) or late AMD in 1 eye and for whom DNA samples were available. The baseline AMD severity levels in these 867 individuals matched guidelines for therapy with the AREDS supplement. Single nucleotide polymorphisms (SNPs) in the *CFH* (p.Y402H, rs1061170) and *ARMS2* (p.A69S, rs10490924) genes were genotyped. Evidence for a possible interaction between the *CFH* genotype and the benefit of treatment with antioxidants plus zinc was detected. Individuals with the homozygous nonrisk genotype for *CFH* (TT) had a greater reduction in progression to late AMD than those with the homozygous risk genotype (CC), 68% versus 11% ($P = 0.03$). There was no significant interaction between *ARMS2* p.A69S genotype and treatment with any AREDS supplement regimen. Results of their study led Klein et al[20] to conclude that AREDS supplements were associated with a reduction in progression to late AMD in all genotypic groups and that neither antioxidant alone nor zinc alone was superior to the combination of antioxidants and zinc in reducing progression to AMD in any genetic group. Although evidence for differences in treatment response to AREDS supplements for individuals with different genotypes was observed, the results for all groups were in the direction of a treatment benefit. These findings, together with the need for replication data and corroborative functional studies and the lack of available alternative interventions, led the authors to conclude that routine genetic testing was not indicated before prescribing AREDS supplements.

A more recent study by Awh et al[21] suggested that the administration of AREDS supplements should be modified in certain subgroups of patients based on their *CFH* and *ARMS2* genotypes. The present study examined a subset of the AREDS participants (n = 995) from whom DNA was collected. We re-evaluated this suggestion in an unplanned retrospective analysis of a larger cohort of AREDS participants (from 1237 to 1413, depending on the SNPs) with available DNA and who were at high risk of late AMD developing.

Methods

Study Population

The AREDS design was reported previously.[22] We summarize the study details that are relevant to this report. Participants with varying severities of AMD were enrolled in 11 retinal specialty clinics. Each clinical center obtained institutional review board approval for the study protocol, and all participants signed the