

AMD Risk Alleles Predict Response to Nutritional Supplementation

Genotype-directed nutritional therapy could result in improved outcomes for individuals with moderate AMD.

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The landmark Age-Related Eye Disease Study (AREDS)¹ established that nutritional supplementation with a combination of antioxidants and zinc decreases the risk of progression to advanced age-related macular degeneration (AMD) in individuals with at least moderate AMD. At present, nutritional supplementation with the AREDS formulation of high-dose antioxidants plus zinc is the only evidence-supported means of reducing the risk of developing advanced AMD.

In participants receiving the AREDS formulation, the 5-year risk of progression from intermediate to advanced AMD was reduced by 25%, and moderate vision loss among those at high risk of developing GA or choroidal neovascularization (CNV) was reduced by 19%.

Since 2005, a number of genetic risk factors for AMD have been identified. These include variants in the gene for complement factor H (CFH)²⁻⁵ and the age-related maculopathy susceptibility 2 (ARMS2) gene.^{6,7}

The biologic features of these genetic risk factors for AMD suggest that they may have interactions with components of the AREDS formulation. For example, CFH binds zinc, neutralizing its ability to inhibit complement component 3b (C3b).⁸⁻¹⁰ The ARMS2 protein is localized in mitochondria, where it may have an effect on the interaction of antioxidants with free radicals.¹¹⁻¹²

With these potential interactions in mind, a pharmaco-

genetic analysis of AREDS patients was performed to determine whether these or other genetic risk markers influence the response to nutritional supplements in individuals with AMD.¹³ Examining genetic markers that account for almost all known population-attributable risk, investigators sought to identify groups for whom specific nutritional supplements were beneficial or harmful.

This analysis, which was published online this year,¹³ and which was first presented at the American Society of Retina Specialists Annual Meeting in Toronto, Canada, indeed found that individuals with moderate AMD can potentially benefit from pharmacogenomic-based selection of nutritional supplements. This article recounts in brief some of the factors analyzed in that study and their implications for patients with AMD.

STUDY DESIGN

The AREDS dataset was obtained from the National Center for Biotechnology Information's database of Genotypes and Phenotypes (dbGaP; <http://www.ncbi.nlm.nih.gov/gap>).

AREDS patients had been categorized at enrollment, through retinal images graded at a central reading center, into 1 of 4 categories: (1) no AMD: fewer than 5 small drusen; (2) mild AMD: multiple small drusen, nonextensive intermediate drusen, pigment abnormalities, or

a combination; (3) intermediate AMD: at least 1 large druse, extensive intermediate drusen, or noncentral geographic atrophy (GA); and (4) advanced AMD: central GA or neovascular AMD in 1 eye, or visual loss resulting from AMD. All participants in category 2 and higher were randomized to 1 of the 4 types of dietary supplement: placebo, antioxidants, zinc, or antioxidants plus zinc (the AREDS formulation).

AREDS enrolled 4757 patients. Because the genetics of AMD has been best studied in white patients, those with other ethnic backgrounds were excluded from this analysis. Analysis was limited to white patients with AREDS category 3 disease in at least 1 eye and AREDS category 1 to 4 disease in the other eye (n=2258; dubbed the AREDS set). Available DNA samples were obtained from the Coriell Institute, the repository for AREDS DNA, for 995 of these patients (the sample set). Genotyping was performed on these samples using bidirectional sequencing.

The sample set was compared with the AREDS set to ensure that it constituted a representative group of patients with moderate AMD. Other than a 0.6 year difference in age, there were no significant differences in nongenetic risk factors, treatment group distribution, average AREDS simplified severity score, or proportion of CFH and ARMS2 risk alleles, between the 2 sets.

Statistical analysis was performed as follows. First, patients were grouped by their AREDS-assigned treatment category. Next, a forward stepwise Cox regression analysis was used to identify any genetic or nongenetic risk factors significantly associated with progression to advanced AMD within each treatment group. Then, a treatment-group-specific Cox proportional hazard regression analysis was used to analyze the impact of these identified risk factors on progression in each treatment group.

RESULTS

Numerous genetic and nongenetic factors were analyzed in the forward stepwise Cox regression analysis to evaluate their impacts on AMD progression in each treatment group. Of the genetic factors analyzed, the only ones that had a statistically significant impact on treatment groups were as follows: for placebo treated patients, only CFH and ARMS2 risk alleles; for antioxidants, only ARMS2; for zinc, only CFH; and for antioxidants plus zinc, only CFH and ARMS2.

Cox proportional hazard regression analysis was then used to evaluate the impact of these risk factors within each treatment group. The calculated risk ratios were the major outcome of the study and demonstrated that these risk alleles had a substantial and additive impact

TABLE 1. COX REGRESSION ANALYSIS WITHIN TREATMENT GROUPS

Treatment Group	Risk Ratio	p value
Antioxidants		
ARMS2 1 allele	2.581	5.749E-05
ARMS2 2 alleles	3.963	2.219E-06
Zinc		
CFH 1 allele	2.184	4.161E-02
CFH 2 alleles	4.461	7.522E-05
Antioxidants + zinc		
CFH 2 alleles	1.833	1.026E-02
ARMS2 2 alleles	1.887	8.540E-04
C=CFH; A=ARMS2		

TABLE 2. POSSIBLE GENOTYPE COMBINATIONS OF CFH AND ARMS2

Risk Markers	CFH0	CFH1	CFH2
ARMS0	C0A0	C1A0	C2A0
ARMS1	C0A1	C1A1	C2A1
ARMS2	C0A2	C1A2	C2A2
C=CFH; A=ARMS2			

on progression in each treatment group (Table 1).

These risk ratios were then used to estimate the absolute risk of AMD progression for each treatment group. For each treatment (zinc, antioxidants, zinc plus antioxidants, and placebo) and each possible genotype combination (Table 2), excess risk was determined for specified projected time intervals.

For participants receiving zinc only, the calculated disease progression rate increased as a function of the number of CFH risk alleles. Patients with 1 or 2 CFH risk alleles derived no benefit from treatment with zinc or with antioxidants plus zinc. Progression in the zinc-only group was not affected by the number of ARMS2 risk alleles.

The converse was true for patients receiving antioxidants only. Progression rate increased as a function of the number of ARMS2 risk alleles. Progression in the antioxidants treatment group was not affected by the number of CFH risk alleles.

Patients with 2 copies of both CFH and ARMS2 risk alleles fared relatively poorly, and minimal benefit was derived from any therapy. Approximately three-quarters of participants with 2 copies of each risk allele progressed to advanced AMD at 12 years, a progression rate twice that of patients with no risk alleles.

TABLE 3. OPTIMAL AREDS-ASSIGNED TREATMENTS AS A FUNCTION OF CFH AND ARMS2 RISK ALLELES

CFH	ARMS2	Best Treatment	Study Population Frequency (%)
0	0	-	5.86
0	1	zinc	5.26
1	0	AO	22.5
0	2	zinc	1.01
1	1	AO plus zinc	22.6
2	0	AO	13.3
1	2	zinc	6.57
2	1	-	16.4
2	2	-	6.67

Treatment with the lowest progression rate for each genetic risk profile is shown. Frequency of each genetic risk profile in the study population is at right. CFH = complement factor H; ARMS2 = age-related maculopathy sensitivity 2; AO = antioxidants

TREATMENT IMPLICATIONS

By analyzing the results in patients with different genotypes receiving different assigned treatments in AREDS, it is possible to generate a list of optimal treatments for each genotype combination (Table 3). When the relative frequency of these genotype groups within the sample population is considered, it is notable that the optimal treatment regimen for approximately 49% of patients is something other than the AREDS formulation.

Based on these calculated progression rates and the relative frequency of these genotypes, if all the AREDS sample set patients had been treated with genotype-directed therapy, the 10-year progression rate to advanced AMD could have been reduced by 33% compared with placebo, vs a 14% reduction if all had been treated with the AREDS formulation. That is, based on this pharmacogenetic analysis, genotype-directed therapy would have more than doubled the reduction in AMD progression seen with the AREDS formulation.

In 2003, the AREDS Research Group projected that if all people at risk for advanced AMD received the AREDS supplement, more than 300 000 patients would avoid progression to advanced AMD during the following 5 years.¹⁴ The impact of doubling this benefit, both in terms of quality of life for affected patients and savings to the health care system, would be substantial.

CONCLUSIONS

This pharmacogenetic analysis found that CFH and ARMS2 genetic risk markers predict response to antioxidants and zinc in patients with moderate AMD. The analysis led to the following conclusions regarding patients with AREDS category 3 disease in 1 eye and category 1 to 4 disease in the other eye:

- The AREDS formulation was of maximum benefit for patients with 1 CFH risk allele and 1 ARMS2 allele (C1A1).
- With the exception of patients with genotype C1A1, zinc supplementation was of maximum benefit for patients with no more than 1 CFH risk allele and at least 1 ARMS2 risk allele.
- Antioxidant supplementation was of maximum benefit for patients with at least 1 CFH risk allele and no ARMS 2 risk alleles.
- No benefit was seen with any combination of supplementation in AREDS for patients with genotypes C0A0, C2A1, or C2A2.

The identified interactions are biologically plausible. The authors concluded that genotype-directed nutritional therapy could result in improved outcomes for individuals with moderate AMD. ■

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