AMERICAN ACADEMY OF OPHTHALMOLOGY®

Correspondence

Re: Genetic polymorphisms of *CFH* and *ARMS2* do not predict response to antioxidants and zinc in patients with age-related macular degeneration (*Ophthalmology*. 2018;125:391-397)

TO THE EDITOR: We requested that the National Institutes of Health Agency of Intramural Research Integrity investigate the use of the National Eye Institute's position of authority to advance its commercial interest in the Age-Related Eye Disease Study (AREDS) formulation. A statistical review was commissioned and is reported, in part, in the publication by Assel et al.[1] As part of the review process genotypes from 535 AREDS cases that were not analyzed in the publications that first highlighted potential genotype-specific harm and previously unavailable were provided.[2] This subject set has been considered a validation set by Assel et al.[1]

Since early work on the interaction of genetics and the AREDS formulation an influential publication by Seddon et al,[3] reported that both *CFH* and *ARMS2* genotypes interacted with the AREDS formulation when choroidal neovascular disease was considered as a progression event.[2,3] This finding was consistent with observations of the original AREDS investigators, who concluded that nutritional supplements that prophylax against choroidal neovascularization (CNV) are comparatively ineffective in preventing geographic atrophy.[4] Assel et al[1] considered either geographic atrophy or neovascular disease as progression events as a relevant progression event, which has limited their findings.

We used AREDS data files to identify the time to first progression to CNV separately from progression to any type of advanced age-related macular degeneration using the 535 validation cases considered by Assel et al. Recommendations for individuals with 2 *CFH* risk alleles and no *ARMS2* alleles (Genotype Group [GTG]2) are central to the clinical usefulness of genetic testing. The progression phenotype is provided in 2 data fields within the AREDS datasets—AMDSEVRE and AMDSEVLE.[5] For 75 GTG 2 cases from the Assel et al validation set, the power to detect a hazard ratio (HR) of 2.5 at an alpha of 0.05, is only 49%, as calculated by the R package powerSurvEpi, so effect sizes must be greater than this to be detected more than one-half the time. We determined that the HR for progression to any advanced age-related macular degeneration in this group is not significant (HR, 1.04; $P = 0.94$) as correctly stated by Assel et al. When CNV is considered as an end point, the picture is quite different. The HR is 6.4 ($P = 0.015$). Multiple testing statistical significance threshold correction is not appropriate for a validation analysis. Using genotypes provided by the AREDS investigators, the reciprocal genotype group to the one harmed can be analyzed in a similar fashion. Among 110 subjects in GTG 3, the HR for progressing to any advanced age-related macular degeneration is 0.72 ($P = 0.29$). When CNV is considered as an outcome, the HR is 0.39 ($P = 0.015$) (Fig 1).

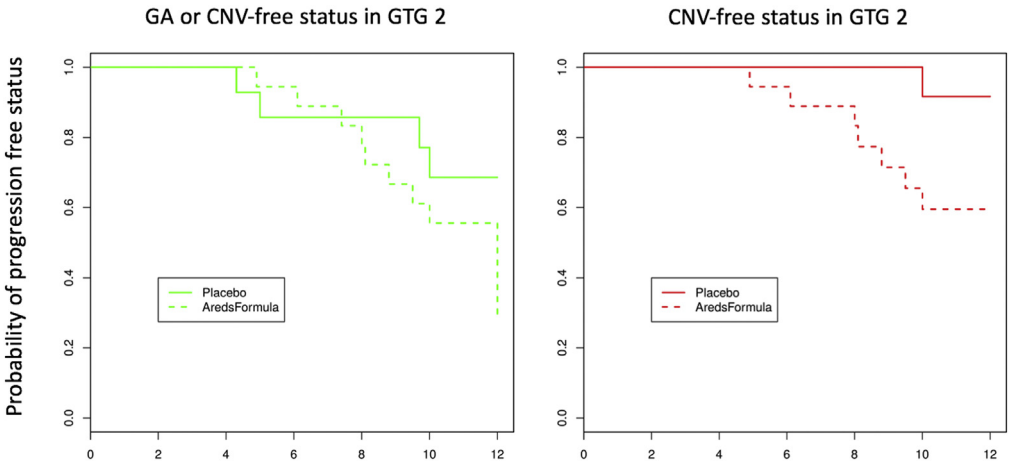

Figure 1. Cox proportional hazard estimate of the proportion of Genotype Group 2 (GTG2) individuals remaining free of geographic atrophy (GA) or neovascular disease (*left*), or just neovascular disease (*right*) using the 535 patient validation set of Assel et al. New patient data provided by the National Institutes of Health in conjunction with the work by Assel et al that underscores the distinction between GA and choroidal neovascularization (CNV) as distinct progression phenotypes validates previous observations. The GA end point is not relevant for AREDS prophylaxis and should be removed from the statistical analyses. Some patients benefit (GTG3) and some may be harmed (GTG2).

The primary genotyping data and a study phenotype abstraction with statistical R code for performing these calculations on this validation set is available at www.aaojournal.org. These files should be considered an extension of this letter and can be used by anyone to independently study this important validation set (Genetic and phenotypic data and Assel data; www.aaojournal.org).

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Available online: ■■■.

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