Genetic Screening & the Response to AREDS Supplementation

Summary

ScienceBased Health (SBH) has evaluated the available evidence regarding the genetic testing of AMD patients for the purpose of 'tailoring' Age-related Eye Disease Study (AREDS) supplements based on an individual's genetic risk profile. SBH sought the opinion of experts in the field of AMD genetics, as well as an independent assessment by Elizabeth Johnson, PhD of the USDA Human Nutrition Research Center on Aging, and Professor, Friedman School of Nutrition and Science Policy at Tufts University.

Only two studies have examined whether genotype in high-risk AREDS participants influences their response to treatment with zinc and/or antioxidants. The results and conclusions of these studies differ greatly. Due to the inconsistent methods and results, as well as the limited sample sizes in the two studies, we conclude that there is currently insufficient information to personalize recommendations for supplement use based on genotype. SBH, therefore, has no plans to offer "antioxidants only" or "zinc only" formulations for AMD patients at this time.

Introduction

The field of nutrigenetics studies how an individual's genetic makeup affects the response to diet and the susceptibility to diet-related diseases. This involves identifying gene variants associated with different responses to nutrients and with higher susceptibility to diet-related diseases. Genetic markers are used in these studies, and are sequences of DNA that have been traced to specific locations on chromosomes. Genetic markers are associated with particular traits and can be different among individuals. Ultimately, the goal of nutrigenetics is to provide nutritional recommendations for individuals to decrease their risk of disease.

Nutrigenetics has been studied in AREDS. The two genes that have consistently been shown to have the strongest associations with AMD are the complement factor H (*CFH*) gene and the Age-Related Maculopathy Susceptibility 2 gene (*ARMS2*). *[See the last section, Background Information for terminology and more about these genes].* Both genes have recently been evaluated for their interaction with the AREDS supplement on progression from intermediate to advanced AMD in AREDS participants.

Contrasting Study Findings

In the earlier of these two investigations, Klein et al.[1] report that supplementation with AREDS antioxidants plus zinc resulted in a greater reduction in AMD progression (68%) in those with the low-risk genotype for CFH than in those with the high-risk genotype (11%). This interaction was primarily related to the zinc component of the supplement. While the major benefit of zinc and antioxidants was seen in patients with the low-risk CFH genotype, all CFH genotypes (both high and low risk) benefited from zinc and antioxidants. Importantly, no harm was seen in those with CFH risk alleles. The authors also found no association between AREDS treatment assignment and having ARMS2 risk alleles.

The second study by Awh et al.[2] also examined whether CFH and ARMS2 genotypes influence treatment response to AREDS supplements. The findings, however, contrast with those of Klein et al. While Awh et al. note that antioxidant treatment was associated with a decreased risk of disease progression in patients with CFH risk genotypes, they report an increased risk of disease progression associated with zinc treatment. The opposite relationships were observed for the ARMS2 risk genotypes: maximum benefit was associated with zinc supplementation, while a deleterious response was associated with antioxidant supplements.

Why the Discrepancy in Findings?

There are several major concerns regarding the Awh et al. paper that may explain the inconsistent findings of these two studies. First, Awh and colleagues evaluated different genetic markers for the CFH and ARMS2 genes than Klein and his fellow researchers.

It would have been both valuable and customary for Awh et al. to evaluate the markers described in the earlier Klein et al. publication. Awh and colleagues had knowledge of the markers used and the associations found by Klein and his group. Yet the Awh publication states that they evaluated certain markers and not others for "technical reasons", with no further explanation provided.

Secondly, Awh et al. did not take into account other variables among the genetic marker groups that could have affected the results of their analyses. Potential confounders such as smoking, age and body mass index may have differed among genotypes, and failure to adjust for these factors could have impacted the study results. (The investigators only considered these factors when comparing the sub-population they were evaluating – AREDS category 3 participants—to the total AREDS population, for which there were no significant differences).

Both of these studies had limited sample sizes. Additionally, the results of either study cannot be generalized. These analyses were performed in patients at risk for progression to advanced AMD – i.e. white people with intermediate AMD. This population may differ in many respects to the general public. No conclusions can be drawn for the benefit/risk of the AREDS supplement for the population as a whole based on their genotype. And, considering the pressing need for further research, it's premature to recommend routine genetic testing for high-risk AMD patients to predict their response to antioxidants and/or zinc supplementation.

References:

1. Klein ML et al. CFH and LOC387715/ARMS2 genotypes and treatment with antioxidants and zinc for age-related macular degeneration. Ophthalmol 115:1019-1025, 2008.

2. Awh CW et al. CFH and ARMS2 Genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. Ophthalmol Aug. 20, 2013 [Epub ahead of print].

Background Information

Definitions:

Allele – One of a number of alternative forms of a gene that is located at a specific position on a particular chromosome.

Genetic marker – DNA sequence with a known location on a chromosome. Genetic markers can help link an inherited disease with the responsible gene. DNA segments close to each other on a chromosome tend to be inherited together. Genetic markers are used to track the inheritance of a nearby gene that has not yet been identified, but whose approximate location is known. The genetic marker itself may be a part of a gene or have no known function.

SNP – A site in the genome where a single DNA nucleic acid base (C, G, T or U) often differs from person to person; SNP stands for Single Nucleotide Polymorphism. Some, but not all SNPs appear to be associated with variation in different people's phenotypes (i.e. their observable biochemical or physical traits).

The CFH and ARMS2 Genes

The CFH gene encodes a protein that regulates a part of the immune system known as the complement system. The complement system helps clear pathogens and cellular debris. However, the complement system can lead to chronic, cell-damaging inflammation if uncontrolled. The CFH protein provides a crucial brake on the complement system that is triggered in response to elevated levels of C-reactive protein (CRP). CRP is normally recruited to sites that might be susceptible to pathogens.

Variations in the SNP in the CFH gene affect a region of the CFH protein that is important for binding to CRP. Studies have shown that people with the riskier version of this SNP make an altered version of the CFH protein with a reduced ability to bind to CRP. Excess levels of CRP may lead to an overactive complement system that damages ocular tissues. The finding by Klein et al that the major benefit of zinc and antioxidants is to those with low-risk rather than high risk CFH suggests that these nutrients have limited effects in those who inherit a stronger predisposition for AMD.

While the CFH SNP appears to be a major genetic risk factor for AMD, less is understood about the mechanism by which LOC387715/ARMS2 gene affects AMD risk. Unlike CFH and other genes that have been associated with AMD, ARMS2 is not part of the complement system. It appears to be turned on within mitochondria, and it may be involved in mitochondrial function and the production of oxygen free radicals.