Special Issue

Genetic and Environmental Underpinnings to Age-Related Ocular Diseases

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Submitted: September 9, 2013
Accepted: September 27, 2013

Citation: Seddon JM. Genetic and environmental underpinnings to age-related ocular diseases. *Invest Ophthalmol Vis Sci*. 2013;54:ORSF28–ORSF30. DOI:10.1167/iovs.13-13234

Age-related macular degeneration (AMD), cataract, glaucoma and diabetic retinopathy are common causes of visual loss. Both environmental and genetic factors contribute to the development of these diseases. The modifiable factors related to some of these age-related and visually threatening diseases are smoking, obesity, and dietary factors, and a cardiovascular risk profile. Many common and a few rare genetic factors are associated with AMD. The role of genetic variants for the other diseases are less clear. Interactions between environmental, therapeutic, and genetic factors are being explored. Knowledge of genetic risk and environmental factors, especially for AMD, has grown markedly over the past 2.5 decades and has led to some sight-saving approaches in preventive management.

Keywords: environment, genetics, age-related eye diseases, ORSF symposium

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the United States, and the prevalence of AMD is expected to increase by up to 97% 2050.[1–3]

AMD adversely affects quality of life and activities of daily living, and leads to loss of independence in retirement years.[4] This complex disease has both environmental and genetic contributing factors. Modifiable factors include smoking and overall abdominal obesity and dietary factors, including antioxidants and dietary fat intake.[2,5] Several common genetic variants with small to moderate impact and recently discovered rare genetic variants with much stronger effect are known to lead to the development and progression of AMD.[5–9] The knowledge of epidemiologic and genetic factors gained over the past 2 decades has formed the scientific basis for new ways to prevent and manage this prevalent disease.

Relative Contribution of Genetic and Environmental Factors

The large population-based twin study of more than 12,000 World War II veterans in the National Academy of Sciences-National Research Council Twin Registry, found that genetic factors explain 46% to 71% of the occurrence of the disease, with the highest heritability for the more advanced forms of AMD and environmental exposures accounting for approximately 19% to 37% of the variance (Ref. 10 and Seddon JM, et al. *IOVS* 1997;38:ARVO Abstract S676). Similar results were seen in a survey of female twins.[11]

Environmental Factors

Smoking is an avoidable risk factor for AMD. In a prospective cohort study, smoking 25 or more cigarettes per day (approximately a pack) and past smoking increased risk of incident AMD more than 2-fold compared with never smokers.[2,5] Nutritional factors are known to modulate the risk of AMD and its progression. The initial study to systematically evaluate the relationship between dietary intake and nutritional factors and AMD showed a protective effect of dietary lutein and zeaxanthin on risk of neovascular AMD.[12] The highest quintile of intake was associated with a 43% reduction in risk, and frequent consumption of spinach and collard greens, high in these carotenoids, markedly reduced risk. Beta-carotene derived from food intake did not reduce risk of AMD. Some studies have confirmed these findings and showed similar effects. The Age-Related Eye Disease Study (AREDS)[13] later found that antioxidant and mineral supplements reduced risk of progression from intermediate to advanced levels of AMD. AREDS2 compared a modified AREDS1 formula to the original or modified AREDS formula referred to as "placebo" in the primary analyses, which did not show added benefit.[14] In subgroup analyses, there was a statistically significant reduced risk of progression to advanced AMD for lutein and zeaxanthin supplements among participants with low dietary lutein and zeaxanthin intake. The AREDS group recommends lutein plus zeaxanthin supplements rather than beta-carotene supplements for prevention of AMD. Higher total dietary fat intake increases risk of progression to advanced AMD almost 3-fold for the highest dietary fat intake compared with the lowest intake. In contrast, a diet rich in omega-3 fatty acids has been shown to be protective in several studies with a reduction in risk of 30% to 50%.[2,5,15] The proposed mechanisms through which omega-3 fatty acids may exert a protective effect on macular degeneration include antioxidative, anti-inflammatory, and antiangiogenic effects.

AMD and cardiovascular disease (CVD) share common antecedent risk factors.[16] In addition to smoking and diet, overall obesity and abdominal adiposity are also important modifiable factors. Higher BMI and waist circumference increase risk of progression, and vigorous physical activity

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reduces risk.[2,5] There is some evidence linking cholesterol level to AMD, but the results have been inconsistent. Inflammation plays a central role in the pathogenesis of drusen and AMD. C-reactive protein (CRP) is a marker for systemic inflammation as well as cardiovascular disease, and homocysteine is an amino acid that adversely affects the vascular endothelium. CRP serum levels are significantly elevated in individuals with advanced AMD, adjusting for age, sex, body mass index (BMI), and smoking,[17] and higher levels increase risk of progression. Higher homocysteine levels may also be associated with AMD. Serum CRP and homocysteine were associated with dietary and behavioral risk factors for AMD.[18] Increased plasma levels of complement activation fragments Bb and C5a were also independently associated with advanced AMD and these complement markers are related to smoking and higher levels of BMI.[19]

Genetic Factors

AMD is a common, complex disease with numerous associated AMD genetic loci. These genetic factors have small to moderate effects on risk and increase susceptibility to the disease in addition to environmental factors, and the heritablilty is as high as 71% in advanced cases (Ref. 10 and Seddon JM, et al. *IOVS* 1997;38:ARVO Abstract S676). Genetic linkage studies found several peaks in many chromosomes, including 1 and 10 where the initial AMD genes were located. Candidate gene studies based on genes associated with macular and retinal Mendelian diseases were done, but did not yield strong or consistent results.

Since 2005, at least 20 known genes have been confirmed for AMD.[9] Many are in the complement pathway. Some genes play a role in pathways related to high-density lipoprotein cholesterol, collagen, and extracellular matrix and angiogenesis,[20,21] and the pathway is not yet known for several genes. Rare, highly penetrant mutations also contribute to AMD risk, including *CFH* R1210C, which is one of the first instances in which a common complex disease variant led to the discovery of a rare penetrant mutation and the first one reported for AMD.[7] Rare variants in the genes *C3*, *CFI*, and *C9* also confer high risk of AMD.[8,22] Genes also increase rates of progression to advanced stages and transitions between stages.[23,24] Gene-environment studies of the *CFH* locus provided early evidence that modifiable factors can alter genetic susceptibility.[25] Response to AREDS supplements may also be related to *CFH* genotype and supplementation was less beneficial for the *CFH* Y402H homozygous risk genotype.[26,27]

Combination of Genes and Environment

There is an interaction between docosahexaenoic acid intake and *ARMS2/HTRA1* on risk of developing geographic atrophy (GA).[15] Smoking increases risk for all *CFH* and *ARMS2/HTRA1* genotypes.[5,14,23] In monozygotic twins discordant for signs of AMD, smoking was heavier for the twin with the more advanced stage of AMD and dietary intakes of betaine and methionine were higher for twins with less advanced AMD.[28] These effects of smoking and diet suggest that epigenetic changes can modify gene expression and lead to different phenotypes in genetically identical individuals. Methylation changes were also evaluated in a small study of AMD-discordant twin pairs.[29]

Predictive models have been developed using an algorithm to create a risk score combining the effects of demographic, behavioral, macular, and genetic factors on risk of progression to advanced AMD from no maculopathy or early and intermediate disease.[27,30] For example, an individual with large drusen in both eyes with a high-risk profile has a 60% chance of progressing over 10 years to advanced AMD based on the predictive algorithm, whereas a person with the same fundus findings and a low-risk profile has a 20% chance of progression.[30] Validation of the predictive model indicates the model is useful for clinical studies.[31]

There has been marked progress over the over the past few decades regarding the environmental and genetic underpinnings of AMD, which has formed the scientific basis for the preventive management of AMD. Genetic factors lead to various levels of susceptibility and the environment modifies the effects of this predisposition to varying degrees depending on the level of genetic risk. Genotyping may become a useful tool for identifying individuals who are at high risk for disease and who may therefore benefit from increased surveillance and personalized treatment strategies. The discovery of genetic and environmental mechanisms provides targets for new therapies. Risk prediction models will facilitate clinical trials of these potential treatments with reduced sample size and lower costs.[30]

Diabetic Retinopathy

Diabetic retinopathy is another common cause of visual impairment that is increasing in developing countries. Environmental factors play a large role in the development of type 2 diabetes, most notably diet and obesity. Heritability has been estimated as high as 52% for the advanced form of proliferative retinopathy with retinal neovascularization. However, genetic studies have not yet identified large or consistent genetic susceptibility loci for this disease.[32]

Glaucoma and Cataract

Glaucoma and cataract are common diseases of aging, which are reviewed in other sections of this supplement. Smoking is a known risk factor for cataract.[33] Environmental risk factors for glaucoma are less conclusive. Genetic studies have suggested some susceptibility loci with small effects. Larger studies with well-defined phenotypes may lead to more insight into the genetics of these diseases.

Unmet Needs and Opportunities

All of these diseases provide an opportunity for improved preventive management and better therapies.

Great strides have been made for AMD in terms of prevention, slowing progression, and treatment of the neovascular form of the disease. However, treatments can be improved for the neovascular forms of AMD and need to be developed for the dry stages. Diabetic retinopathy can be reduced with cultural and lifestyle changes and behavioral modification, as well as improved therapeutic targets. Glaucoma requires elucidation of more definitive environmental and genetic factors to enable earlier diagnosis, prevention, and intervention. Cataract has a successful surgical intervention, but preventive measures and other types of therapies could provide enormous economic benefit.

Acknowledgments

Supported in part by R01-EY11309 from the National Institutes of Health, Massachusetts Lions Eye Research Fund, Inc., a Research to Prevent Blindness Challenge Grant to the New England Eye Center, Department of Ophthalmology, Tufts University School of Medicine, the Foundation Fighting Blindness, and the Macular

Degeneration Research Fund of the Ophthalmic Epidemiology and Genetics Service, New England Eye Center, Tufts Medical Center, Tufts University School of Medicine.

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