Applying Genetic Risk Data to Clinical Practice

A predictive test may help in identifying the risk of developing advanced AMD.

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The most common form of acquired human vision loss may also be the most predictable, thanks to research into the genetic nature of age-related macular degeneration (AMD). Most of the risk of AMD-associated choroidal neovascularization (CNV) is related to inherited genetic features that have been elucidated only since 2006.

Human genetic variation can be found in the primary code sequence of DNA (sequence variability), in the number of copies of key parts of the genome (copy number variability), and in biochemical modification of controlling regions of the genome (epigenetic variability).[1,2] With deeper understanding of the structure and the nature of DNA variability and the rapidly falling cost of determining such variability, the contribution of inherited genetics to common human diseases is being elucidated. Early attempts to identify disease-associated variation involved the selection of variations within candidate genes to conduct classic case-control studies. Technical evolution has allowed more than a million sites of variability distributed over the entire genome to be inexpensively measured and variations associated with specific diseases to be determined in an unbiased fashion.

Both the candidate gene approach and genome-wide association studies (GWAS) have been used to elucidate sequence variation associated with AMD.[3] Early work identified the potential importance of the complement family of inflammatory proteins in AMD on the basis of biochemical analysis of retinal drusen. As the genes and naturally occurring sites of variability for all the complement cascade proteins became known, statistically significant associations with neovascular AMD were identified. To date, convincing and reproducible association of variations in the complement factor H (CFH), complement factor I (CFI), complement factor B (CFB) and complement component (CC3) genes have been demonstrated.[4-10] The strongest associated among these, CFH, when present in risk forms on both the maternal and paternal chromosome, confers significant risk, with odds ratios reported to be as high as 15 when compared with individuals without any risk alleles.[11] In comparison, smoking as a risk factor for lung cancer is not as predictive, with an odds ratio of 9.1.

Genome-wide association studies have identified cholesterol-metabolizing genes as risk factors for late stage AMD, consistent with the presence of this molecule in drusen. Variations in hepatic triglyceride lipase (LIPC), ATP-binding cassette transporter 1 (ABCA1), lipoprotein lipase (LPL), and cholesterol ester transfer protein (CETP) are all associated with neovascular AMD.[12,13] Xanthophills, such as zeaxanthine, mesozeaxanthine, and lutein are transported across lipid bilayer membranes by high-density lipoprotein cholesterol,[14] suggesting a link between cholesterol metabolism and macular pigments. Dietary deficiency of xanthophils is associated with a heightened risk of AMD.[15]

Other strong predictors of AMD risk can be found within the mitochondrial genome; variations have been found within haplotypes J, T and U and in a single SNP found at mitochondrial genome position 4917.[16,17] A gene found on chromosome 10 whose product appears to localize to the mitochondria is associated with AMD when found in a form affecting mRNA stability.[18,19] A small insertion-deletion (indel) polymorphism within the ARMS2 gene is strongly associated with disease with an odds ratio second only to the CFH locus.[19]

CLINICAL EVALUATION OF GENETIC RISK FOR AMD PROGRESSION

AMD is one of the best examples of a chronic degenerative genetic disease discovered to date, with heredity representing over 70% of the risk of developing the disease.[12] Genetic testing can identify individuals with an increased risk for advanced AMD. Early identification of at-risk patients may prevent vision loss or slow the pro-

gression of the disease through individualized treatment based on age and risk level. Frequent monitoring of individuals with an increased risk for advanced AMD may result in early detection of small CNV lesions and may lead to improvement of long-term visual acuity through earlier treatment. Additionally, environmental risk factors can be identified and lifestyle modifications can be made to reduce the risk for developing advanced AMD.

Macula Risk (ArcticDx, Inc., Toronto, Canada) is a commercially available prognostic genetic test for patients diagnosed with early or intermediate AMD. Using an algorithm based upon the complete combination of AMD genes and smoking history, the genetic test identifies those most likely to progress to advanced AMD with vision loss. Tested patients are stratified into risk categories. In this grouping, 20% of patients are predicted to have a higher than average lifetime risk of advanced AMD, with 1% of these falling into a high risk group with a predicted 65% chance of developing geographic atrophy or CNV. The ability to identify patients at risk allows physicians to tailor a management plan more appropriate for individual patients.

COLLABORATIVE SYSTEM

At our practice, Tennessee Retina, we are in the early stages of using the Macula Risk test as part of a collaborative system with primary care eye doctors. The goal of this partnership is to identify patients at increased risk of vision loss due to AMD. We hope to develop management algorithms to reduce the risk of disease progression and to increase the chances of earlier detection of neovascular AMD.

For example, a typical patient seen in a primary eye care doctor's office might be aged 70 years with a few intermediate soft drusen in each eye (AREDS category 2) and excellent vision. Acceptable follow-up for such a patient might be a return visit in 1 year. What if, however, genetic testing reveals this patient to be in the highest genetic risk category? Certainly, it would be reasonable to recommend more frequent examinations. Although the average patient sharing this phenotype was not shown to benefit from nutritional supplements in AREDS, it might also be reasonable to suggest supplements for this particular patient. Similarly, use of an Amsler grid or even home preferential hyperacuity perimetry testing (ForeseeHome, Notal Vision, Inc., St. Louis) might be justifiable for the 1% of patients who share this highest degree of genetic risk. The patient's primary care eye doctor might recommend a baseline evaluation by a retina specialist, which is where we enter the picture. Increased awareness among patients and their doctors about AMD should ultimately lead to earlier detection of advanced AMD at a treatable stage.

CONCLUSION

A predictive genetic test for the risk of developing advanced AMD may help clinicians to offer more personalized care for their patients with AMD. Because we know that AMD progression has a strong genetic component, this indication stands to be the first and most durable dividend of chronic disease-directed genetic research. ■

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1. Sachidanandam R, Weissman D, Schmidt SC, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature.* 2001;409(6822):928-933.
2. Bernstein BE, Meissner A, Lander ES. The mammalian epigenome. *Cell.* 2007;23;128(4):669-681.
3. Haines JL, Spencer KM, Pericak-Vance MA. Bringing the genetics of macular degeneration into focus. *Proc Natl Acad Sci USA.* 2007;104(43):16725-16726.
4. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science.* 2005;308(5720):385-389.
5. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science.* 2005;308(5720):419-421.
6. Fagerness JA, Maller JB, Neale BM, Reynolds RC, Daly MJ, Seddon JM. Variation near complement factor I is associated with risk of advanced AMD. *Eur J Hum Genet.* 2009;17(1):100-104.
7. Maller JB, Fagerness JA, Reynolds RC, Neale BM, Daly MJ, Seddon JM. Variation in complement factor 3 is associated with risk of age-related macular degeneration. *Nat Genet.* 2007;39(10):1200-1201.
8. Yates JR, Sepp T, Matharu BK, et al. Complement C3 variant and the risk of age-related macular degeneration. *N Engl J Med.* 2007;357(6):553-561.
9. Francis PJ, Hamon SC, Ott J, Weleber RG, Klein ML. Polymorphisms in C2, CFB and C3 are associated with progression to advanced age-related macular degeneration associated with visual loss. *J Med Genet.* 2009;46(5):300-307.
10. Jakobsdottir J, Conley YP, Weeks DE, Ferrell RE, Gorin MB. C2 and CFB genes in age-related maculopathy and joint action with CFH and LOC387715 genes. *PLoS ONE.* 2008;3(5):e2199.
11. Li M, Atmaca-Sonmez P, Othman M, Branham KE, Khanna R, Wade MS, et al. CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. *Nat Genet.* 2006;38(9):1049-1054.
12. Chen W, Stambolian D, Edwards AO, et al. Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. *Proc Natl Acad Sci U S A.* 2010; 20;107(16):7401-746.
13. Neale BM, Fagerness J, Reynolds R, et al. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC). *Proc Natl Acad Sci U S A.* 2010;107(16):7395-7400.
14. Connor WE, Duell PB, Kean R, Wang Y. The prime role of HDL to transport lutein into the retina: evidence from HDL-deficient WHAM chicks having a mutant ABCA1 transporter. *Invest Ophthalmol Vis Sci.* 2007;48(9):4226-4231.
15. Seddon JM, Ajani UA, Sperduto RD, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *JAMA.* 1994;272(18):1413-1420.
16. Canter JA, Olson LM, Spencer K, et al. Mitochondrial DNA polymorphism A4917G is independently associated with age-related macular degeneration. *PLoS ONE.* 2008;3(5):e2091.
17. Udar N, Atilano SR, Memarzadeh M, et al. Mitochondrial DNA haplogroups associated with age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2009;50(6):2966-2974.
18. Weeks DE, Conley YP, Tsai HJ, Mah TS, Schmidt S, Postel EA, et al. Age-related maculopathy: a genomewide scan with continued evidence of susceptibility loci within the 1q31, 10q26, and 17q25 regions. *Am J Hum Genet.* 2004;75(2):174-189.
19. Fritsche LG, Loenhardt T, Janssen A, et al. Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA. *Nat Genet.* 2008;40(7):892-896.