Title
The coming of age for age-related macular degeneration genetics.

Journal
Ophthalmic genetics, 26(2)

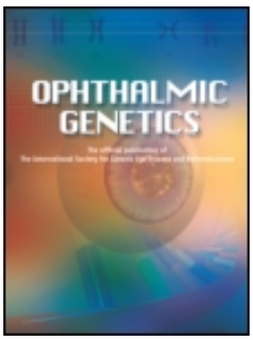
ISSN
1381-6810

Author
Gorin, Michael B

Publication Date
2005-06-01

DOI
10.1080/13816810590969914

Peer reviewed



Ophthalmic Genetics

ISSN: 1381-6810 (Print) 1744-5094 (Online) Journal homepage: http://www.tandfonline.com/loi/iopg20

The Coming of Age for Age-Related Macular Degeneration Genetics

Michael B. Gorin

To cite this article: Michael B. Gorin (2005) The Coming of Age for Age-Related Macular Degeneration Genetics, Ophthalmic Genetics, 26:2, 57-59, DOI: 10.1080/13816810590969914

To link to this article: http://dx.doi.org/10.1080/13816810590969914

Published online: 08 Jul 2009.

Ophthalmic Genetics, 26:57–59, 2005

ISSN: 1381-6810 (print) / 1744-5094 (online)
DOI: 10.1080/13816810590969914

Taylor & Francis
Taylor & Francis Group

EDITORIAL

The Coming of Age for Age-Related Macular Degeneration Genetics

Michael B. Gorin
Departments of Ophthalmology and Human Genetics, University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, PA, USA

In this issue of *Ophthalmic Genetics*, Santangelo and colleagues (pp. 61–67) present a new linkage study of age-related macular degeneration (AMD) using microsatellite markers and discordant sib-pairs. This powerful technique offers an alternative strategy than the affected sib-pair studies and is potentially more robust for different genetic models.[1,2] The method does, however, have limitations for late-onset AMD, because of the possibility that unaffected individuals labeled as unaffected at some age will become affected as they age and recruitment of truly unaffected family members becomes a greater challenge. The investigators reported on 110 extremely discordant sib-pairs from only 40 families, illustrating the difficulty of acquiring and ascertaining these families compared to affected sib-pairs. Though all ascertained individuals were 60 years of age or older, there was no mention in the paper with regard to the distribution of ages among the affected sibs compared to the unaffected sibs, which would provide some additional reassurance regarding misclassification of unaffected individuals. However, the natural history of AMD based on the Age-Related Eye Disease Study[3] indicates that individuals with mild findings of AMD (extensive small drusen, nonextensive intermediate-size drusen, or pigment abnormalities) between the ages of 55 and 80 had only a 1.3% five-year probability of developing advanced AMD.

In agreement with other AMD genetic linkage studies,[4–11] the Santangelo study reported evidence of linkage for loci that were confirmatory to those in multiple other studies, while others appear to be novel. For those who are unfamiliar with genome-wide scans of complex genetic disorders, the partial agreement and variances among these studies can be bewildering. However, studies of AMD genetics have reflected a higher level of agreement than those of nearly every other condition. Replication of linkage loci is sensitive to a number of factors, irrespective of the fact that one generally needs much larger sample sizes for replication studies than for the original study. There is little doubt of the validity for the AMD genetic loci on 1q31 and 10q26, and the recent reports[12–14] of a specific variant of the complement factor H (CFH) gene on chromosome 1q31 using association studies have established the first solid gene that contributes to AMD risk. What about those loci that are reported in some studies and not in others? Even with the increased theoretical power of using discordant sib-pairs, the ability of smaller linkage studies such as that of Santangelo and colleagues to convincingly establish AMD loci is limited. The multipoint LOD scores are not very high and potentially confounded by the problems of multiple testing. One also has to be cautious of comparing these results with those from the prior linkage study reported by this group.[15] Since common families were used in both linkage studies, this study does not represent an independent replicate cohort. Notwithstanding these caveats, when the results are confirmatory of other linkage studies, our suspicion is raised that we are observing a true linkage signal rather than false-positive results. This may be true for loci on 2q31.2-q32.3, 2p, and 6q25.3 and, to a lesser extent, for loci on 19p and 20q. Meta-analyses that combine data from a number of these linkage studies, as well as conditioning existing linkage data on specific genes, such as ApoE and CFH, and environmental factors such as smoking, offer the best opportunities for refining the search for the etiology of AMD using family data. Unless future family studies are extremely large, they will offer only limited confirmatory information. However, such studies may provide useful genotype-phenotype insights as the clinical characterization of the AMD phenotype improves. As shown by the three recent papers in *Science*,[12–14] association methods offer perhaps our best strategy for finding AMD-related genes and variants.

The discovery of the first major causative gene for AMD, CFH, is particularly noteworthy because it unifies the linkage studies performed with AMD families with association studies that were conducted with AMD-affected individuals irrespective of those who have a positive family history. There is little doubt that the familial forms of AMD are neither clinically nor genetically distinguishable from the much larger population of

Accepted 6 April 2005.
Address correspondence to Michael B. Gorin, M.D., Ph.D., UPMC Eye Center, The Eye & Ear Institute Building, 203 Lothrop Street, Pittsburgh, PA 15213, USA. E-mail: text paging: 4123927794@mobilecomm.net

sporadic cases. These recent studies, in conjunction with three additional confirmatory studies[20–22] also establish the feasibility of determining a limited set of genes, which contain variants that confer a significant amount of risk for developing AMD. There will always be a small percentage of AMD cases that will be caused by rare genetic conditions. There is also no guarantee that future association studies will provide such a clear signal for these other AMD loci as was found for chromosome 1q31. These studies are highly dependent on the ancestry of the AMD-related mutations, founder effects, and the stability of the haplotypes in the vicinity of the causative genes. Just as in the original genome-wide linkage scans for AMD and the recent association studies that identified the CFH variant, one will never know until the studies are actually done.

Some authors have already cited the variant of the CFH gene as proof that inflammation and the complement pathway are critically involved in the pathogenesis of AMD. Certainly the work of Hageman, Anderson, and colleagues[16–19] first suggested this hypothesis and they have consistently supported the involvement of complement in early AMD. However, until other AMD-associated genes and variants are identified, we are still at loss for understanding how AMD develops. Genes and their proteins are much like people; their roles and functions at any given moment in time and space are determined by the company with whom they interact. Once the second and third AMD-related genes have been identified, one can then begin to develop risk-assessment models, prospective clinical trials for prevention, and suitable animal models for study. Speculation as to potential candidate genes within areas of AMD linkage is intriguing, but we still know too little about the pathogenesis of AMD to effectively prioritize the hundreds of genes that are within the potential intervals. Purely genetic approaches provide an unbiased strategy that has already proven to be successful. The Santangelo study adds to the growing use of genetics to define complex disorders such as AMD and is part of an exciting period of discovery that will ultimately change our entire understanding and approach to this disease.

ACKNOWLEDGEMENTS

Dr. Gorin gratefully acknowledges the support from NEI R01 EY09859, Research to Prevent Blindness, New York (Senior Scientific Investigator Award), and The Eye and Ear Foundation of Pittsburgh.

REFERENCES

1. Risch NJ, Zhang H. Mapping quantitative trait loci with extreme discordant sib pairs: sampling considerations. *Am J Hum Genet.* 1996;58:836-843.
2. Risch N, Zhang H. Extreme discordant sib pairs for mapping quantitative trait loci in humans. *Science.* 1995;268:1584-1589.
3. Age-Related Eye Disease Study Research G. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* 2001;119:1417-1436.
4. Weeks D, Conley Y, Tsai H-J, et al. Age-related maculopathy: an expanded genome-wide scan with evidence of susceptibility loci within the 1q31 and 17q25 regions. *Am J Ophthalmol.* 2001;135:682-692.
5. Schick JH, Iyengar SK, Klein BE, et al. A whole-genome screen of a quantitative trait of age-related maculopathy in sibships from the Beaver Dam Eye Study. *Am J Hum Genet.* 2003;72:1412-1424.
6. Majewski J, Schultz DW, Weleber RG, et al. Age-related macular degeneration—a genome scan in extended families. *Am J Hum Genet.* 2003;73:540-550.
7. Schmidt S, Scott WK, Postel EA, et al. Ordered subset linkage analysis supports a susceptibility locus for age-related macular degeneration on chromosome 16p12. *BMC Genet.* 2004;5:18.
8. Weeks DE, Conley YP, Tsai HJ, 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;75:174-189.
9. Abecasis GR, Yashar BM, Zhao Y, et al. Age-related macular degeneration: a high-resolution genome scan for susceptibility loci in a population enriched for late-stage disease. *Am J Hum Genet.* 2004;74:482-494.
10. Iyengar SK, Song D, Klein BE, et al. Dissection of genomewide-scan data in extended families reveals a major locus and oligogenic susceptibility for age-related macular degeneration. *Am J Hum Genet.* 2004;74:20-39.
11. Kenealy SJ, Schmidt S, Agarwal A, et al. Linkage analysis for age-related macular degeneration supports a gene on chromosome 10q26. *Mol Vis.* 2004;10:57-61.
12. Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P, Spencer KL, Kwan SY, Noureddine M, Gilbert JR, Schnetz-Boutaud N, Agarwal A, Postel EA, Pericak-Vance MA. Complement factor H variant increases the risk of age-related macular degeneration. *Science.* 2005;308:419-421.
13. Edwards AO, Ritter R III, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. *Science.* 2005;308:421-424.
14. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, Sangiovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J. Complement factor H polymorphism in age-related macular degeneration. *Science* 2005;308:385-389.
15. Seddon JM, Santangelo SL, Book K, Chong S, Cote J. A genomewide scan for age-related macular degeneration provides evidence for linkage to several chromosomal regions. *Am J Hum Genet.* 2003;73:780-790.
16. Mullins RF, Johnson LV, Anderson DH, Hageman GS. Characterization of drusen-associated glycoconjugates. *Ophthalmology.* 1997;104:288-294.
17. Mullins RF, Aptsiauri N, Hageman GS. Structure and composition of drusen associated with glomerulonephritis: implications for the role of complement activation in drusen biogenesis. *Eye.* 2001;15:390-395.
18. Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retinal Eye Res.* 2001;20:705-732.

19. Anderson DH, Talaga KC, Rivest AJ, Barron E, Hageman GS, Johnson LV. Characterization of beta amyloid assemblies in drusen: the deposits associated with aging and age-related macular degeneration. *Exp Eye Res.* 2004;78:243-256.
20. Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, Hageman JL, et al. From the cover: A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci USA*. 2005;102:7227-7232.
21. Zareparsi S, Branham KE, Li M, Shah S, Klein RJ, Ott J, Hoh J, Abecasis GR, Swaroop A. Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. *Am J Hum Genet*. (in press).
22. Conley YP, Thalamuthu A, Jakobsdottir J, Weeks DE, Mah T, Ferrell RE, Gorin MB. Candidate gene analysis suggests a role for fatty acid biosynthesis and regulation of the complement system in the etiology of age-related maculopathy. *Hum Mol Genet*. (in press).