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Gorin, Michael B

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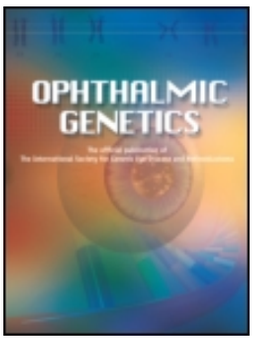

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EDITORIAL

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

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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.

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