AMD Genetic Studies Focus on Alternative Complement Pathway

While this pathway presents potential therapeutic targets, the details of delivery would be challenging.

BY RANDO ALLIKMETS, PHD

Genetic studies in recent years have led to a change in our understanding of age-related macular degeneration (AMD). AMD was traditionally thought to be tied in some way to the aging process and environmental factors, but it is now apparent that genetic mutations are responsible for most of an individual's risk for AMD. Variations in genes governing the alternative complement pathway in the human body's immune system are currently known to account for more than 50% of the risk of developing AMD.

This conception of an inflammation-related etiology of AMD, which has arrived with the blossoming of genomic research in recent years, promises to offer new modalities for diagnostic testing and new targets for therapy. Still, much remains to be learned about exactly how the genes contribute to the disease process.

What do we currently know, and where is this line of research headed? This article attempts to recap the current state of understanding of the genetics of the complement system in relation to AMD and offer some potential directions for future studies.

HISTORICAL PERSPECTIVE

In 2001, Hageman and colleagues[1] proposed that immune-mediated processes played a role in the biogenesis of drusen, the deposits that form between the retinal pigment epithelium and Bruch's membrane that are significant risk factors for the development of AMD. Using an integrated approach synthesizing histochemical, molecular biologic, and other studies, the researchers noted the presence of proteins associated with inflammation and immune-mediated processes in and around drusen and the activation of the complement system in drusen and along the RPE-choroid interface.

The complement pathways, components of the body's innate immune system, involve a number of proteins that work with immune cells and other defenses to fight infections and other triggers. Some complement proteins also stimulate inflammation. The alternative complement pathway can be stimulated by many triggers, not by specific antibodies as the classical pathway is.

In 2005, a banner year in the study of the genetics of AMD, several groups identified variants in the complement factor H gene (CFH) as risk factors for developing AMD.[2-5]

One of these groups, Hageman et al,[2] analyzed the CFH gene in approximately 1,300 individuals in two cohorts in different geographic locations, including approximately 900 subjects with AMD and 400 matched controls. They found multiple variants associated with increased or reduced risk of AMD, including one variant that was present in 50% of AMD cases and 29% of controls (odds ratio = 2.46). Subjects who were homozygous for this variant made up 24% of cases and 8% of controls.

A commentary at the time these multiple studies of factor H were published[6] noted that "This percentage is by far the most impressive 'guilt by association' value obtained thus far for putative AMD-associated genes, which, to date, have typically hovered below 2%."

The following year, investigators looked for associations with AMD in two other genes that encode regulatory proteins in complement pathways.[7] They screened the factor B (BF) and complement component 2 (C2) genes, in the same two independent cohorts including approximately 900 cases and 400 matched controls. One haplotype, which is a combination of genetic variants, was found to be associated with increased risk for AMD, and two variants that were associated with protection against AMD were identified.

These results were then analyzed in combination with the data from the study of CFH.[2] The authors concluded that variations in the three genes, taken together, could predict clinical outcomes in 56% of controls and 74% of AMD cases. That is, 56% of the unaffected control subjects had at least one protective haplotype, and 74% of the patinents with AMD lacked any protective haplotype. Approximately 60% of the risk in affected individuals and 65% of the protection of the control subjects were attributed to the CFH locus, and the rest attributed to the locus containing both BF and C2.

Also in the landmark year of 2005, studies began to identify the locus 10q25 as another genetic region of interest, conferring risk of late AMD, independent of the CFH locus.[8,9] Studies of this locus have been marked by controversy.

WHERE ARE WE NOW?

Although much progress has been made in our understanding of the genetics linking the complement system to AMD, there is still much we do not know. From a geneticist's point of view, we know the alternative complement pathway is involved in a major way, but the specific variants and their functional consequences in complement genes have yet to be identified. There is disagreement about whether it is correct to say that inflammation is involved in the disease process. Immunologists say no, we have not demonstrated the presence of certain cells that must be involved in inflammation. But genetically we know for certain that the alternative complement pathway is involved, and possibly the classical pathway as well—whether we call the result inflammation or a complement-pathway–mediated process.

Commentators have noted that the molecules in the complement pathway will now become potential targets for AMD therapies.[6] However, it remains to be seen what type of therapeutic approach might work. Current AMD treatments focus on a symptom, neovascularization, rather than the cause of the disease. Inhibiting vascular endothelial growth factor (VEGF) production through intravitreal injection of anti-VEGF agents has been shown to work well in the short term, but we do not yet know the long-term effects, both local and systemic, of suppressing this important molecule.

Similarly, the complement system is a vital defense mechanism, both in the eye and throughout the body. Potential therapies aimed at suppressing the complement system could carry serious side effects.

On the other hand, a therapy that promotes protective proteins might be a more promising approach. Remember that researchers have identified protective haplotypes as well as haplotypes that confer increased risk. Injecting a gene that would cause the RPE to produce protective proteins (a "good" complement) might be a more efficacious approach than trying to suppress the production of "bad" complement.

Of course there would be challenges in implementing this type of therapy. Subretinal injection of a therapeutic gene, as has recently been used safely in a small number of patients with Leber's congenital amaurosis (LCA),[10,11] is a far more complex and risky procedure than intravitreal injection of a VEGF inhibitor (See related article on page 50). And AMD is a late-onset disease, so proper timing of this type of therapeutic approach would be more challenging than in an early-onset disease such as LCA. It would probably be necessary to modulate the complement system at an early stage to prevent the disease from developing.

Obviously, much work remains to be done before these recent findings implicating the complement system in the development of AMD can be exploited in the clinic. Still, we know we have an excellent therapeutic target in the complement system, and research continues with the goal of defining the exact disease-related variants and their functions. ■

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