Confluence of research releases flood of AMD genetic data

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RESEARCH by four independent, multidisciplinary groups confirms a long-suspected genetic component to age-related macular degeneration, finding that individuals who carry mutations of a gene for the immunocomplex-modulating Factor H, face a seven-fold increased risk of developing the disease.

While the findings may not offer immediate clinical implications, the research points toward new avenues for investigation that could lead to treatments further down the road, researchers say.

A body of evidence, however, is building about the role infection and inflammation play in AMD.

"It’s great to have such a system that kills invaders, but if it’s not controlled properly it actually does more damage to your tissues probably than the viruses or bacteria would," said Dr. Hageman, who published his results in the April 2005 issue of the Proceedings of the National Academy of Sciences.

He explained that a defective Factor H gene might fail to turn off the system after the infection has been eliminated in such patients, the complement system keeps attacking and attacking because it won’t shut down. Previous studies have shown that the system’s chemicals are present in urine, suggesting a possible connection between an overactive complement system and the development of AMD.

"We have focused for years on the simple idea that if we could determine what drugs are comprised of or where they came from, that could give us insight into the etiology of macular degeneration," said Dr. Hageman.

Case-control genetic association study

To test his hypothesis, Hageman and his team compared the gene in 404 unrelated AMD patients with 131 age-matched controls and 550 AMD patients with 275 age-matched controls.

In addition, the investigators examined the DNA and retinal of 38 human donor eyes with AMD and compared them to 19 healthy controls.

The researchers found that 50% of the AMD patients carried Factor H haplotypes compared to 29% of the healthy controls. Hgt team also identified protective variations of the gene. In other words, people who carried the protective pearls faced a decreased risk in developing AMD.

Carrying the bad gene increases an individual’s susceptibility to developing AMD; it still takes a trigger (like an infection, according to Dr. Hageman. One of his theories is that inflammation hits individuals with the bad gene when they are very young, causing the complement system to become overactive in the back of their eyes. It then could take 50 years to see the ocular results.

"Dr. Hageman’s theory suggests that individuals who carry the changed gene face an overactive complement system with every infection they develop over the course of their life. “That’s our big job now, to figure out what the triggers are,” Dr. Hageman said.

Independent study supports Factor H theory

A second team of researchers used a hypothesis-free approach in their hunt for an AMD gene instead of focusing on one gene, the researchers performed a genome-wide scan of 116,004 DNA sequence variations (SNPs) on a subset of individuals from the Age-related Eye disease Study (AREDS). They reported their findings in the journal Science (2005 APR 15;309(5720):385-389).

The researchers compared the SNPs of 96 patients with AMD to 50 healthy control patients. The group identified one variation that, if carried on both copies of the factor H gene, increased an individual’s risk of developing AMD by 7.4.

"We found this as a result of a very deliberate process.W hen you scan a whole genome, you find things that you would not expect,” said Richard Sackler MD, adjunct professor at the Laboratory of Statistical Genetics at Rockefeller University in New York City. He noted that the fact that other teams also found a correlation between Factor H and AMD validates the finding.

Dr. Sackler and his team want to test their results in different ethnic groups because the present study, like the Hageman project, only included Caucasians. Also, in order to develop treatment, specific underlying biological processes that cause the genetic variation to play a role in AMD need to be determined, according to Dr. Sackler.

"A lot of patients have asked, “Now that we know what gene it is what can we do?” But, I’m at a loss when it comes to defining a treatment in the immediate future. There is still a lot of work to do,” he commented.

His theory is similar to Hageman’s in that the bad gene might cause AMD through either a long-term depletion process or a sudden chain reaction set off by one particularly bad infection.

Emily Chew, MD from the division of epidemiology and clinical research at the US National Eye Institute, reiterated that sentiment, “It (the finding) really helped us open the mechanisms of the disease. Is inflammation an important part of the pathogenesis of macular degeneration? If the inflammation theory is confirmed, the clinical implications might be wide-reaching.

Two additional genetic studies appearing in the same issue of Science (Edwards et al., Haines et al.) investigated genetic associations to AMD. The two independent teams performed their analysis on several independent case-control populations and then focused their genetic linkage analysis on chromosome 1q22. This chromosome has been implicated by past research and happens to be the location of the factor H gene. Both teams identified the same gene change that the Sackler team identified as a major player in AMD. The variation accounts for 20-50 percent of the overall risk of developing the disease, the authors said.

Twin study

In addition to these four genetic linkage studies a twin study provided further interesting insight into the genetics of macular degeneration. In the largest study of its kind, a team of researchers used the classic twin study model in which twins who share all genes (monzygotic) and twins who share only 50 percent of genes (dizygotic) are compared to determine relative heritability of AMD. A 100 percent genetic disease would always occur in both groups of monzygotic twins.

The study was directed by Johanna M Seddon MD ScM, founder and director of the epidemiology unit at Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA. It involved 480 male twins from the National Academy of Sciences-National Research Council-World War II veteran twins registry who were born between 1917 and 1927.

Some 331 of the participants had no AMD signs, 241 had early stage AMD, 162 had intermediate, and 106 had advanced stages of AMD. In the study, 207 of the twin pairs were monzygotic, 181 were dizygotic pairs and 58 were sibs whose twin could not be matched.

Ophthalmologists examined and photographed the subjects and Dr. Seddon graded their AMD signs on a level of 1.5, with 1 being no signs of AMD and 5 being the most advanced stage of AMD. In 55% of the monzygotic pairs in which one twin had AMD, the other twin also had the disease. Yet, in only 25 percent of the dizygotic pairs did one twin have AMD when the sibling had it.

Based on a twin analysis model, genetic factors play a substantial role in the aetiology of AMD and associated macular characteristics, explaining 46 to 71 percent of the variation of the severity of the disease, according to the authors. The research also revealed that environmental factors could account for 19 to 37 percent of the variation in the AMD severity.

"It used to be we thought there might be a genetic component to AMD, now we know. Our results fit together very well with the Factor H gene, as well as our previous finding of a relationship between AMD and C-reactive protein. It provides a good basis for research to look at risk factors that modify genetic susceptibility," said Dr. Seddon.

Other risk factors can be modified

She noted that while there may be no immediate therapeutic spin-off from the current batch of research, being aware of a genetic risk factor could encourage patients to emphasize modifiable factors like smoking and diet.

Taking advantage of the four genetic linkage studies and Dr. Seddon’s study confirm a genetic component and open the door to investigations focusing on the specific biological processes that underlie the development of AMD. But aside from unravelling the biological process that is jumpstarted by genetic susceptibility, researchers will begin to investigate the complex interaction of the gene variation with environmental risk factors known to correlate to the development of AMD. For example, both smoking and high blood pressure have been shown to affect Factor H levels in the blood, Dr. Hageman notes.

He predicted that future AMD research would be able to build on the current findings and could begin to lead to effective treatments. “This gives us real hope that we can tackle this problem.”

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TOPICS

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