Title
Complex Disease: A new vision for age-related macular degeneration

Journal
European Journal of Human Genetics, 13(7)

ISSN
1018-4813

Author
Gorin, Michael B

Publication Date
2005-07-01

DOI
10.1038/sj.ejhg.5201431

Peer reviewed

European Journal of Human Genetics (2005) 13, 793–797

www.nature.com/ejhg

NEWS AND COMMENTARIES

Complex Disease

A new vision for age-related macular degeneration

Michael B Gorin

European Journal of Human Genetics (2005) **13,** 793–794.
doi:10.1038/sj.ejhg.5201431
Published online 27 April 2005

In the March 10 issue of Science, three research groups independently reported evidence of a strong association of the Tyr402His polymorphism in the complement H factor (CFH) gene with the development of a disease that is the leading cause of untreatable blindness in the elderly.[1–3]

Age-related macular degeneration (aka: age-related maculopathy) (AMD) affects nearly 1.75 million individuals in the United States alone.[4] As the proportion of the population that is elderly continues to increase, the prevalence of this condition and its impact on the economic and functional well-being of every society will continue to grow. With a prevalence of advanced AMD features in 1.4% of the population over the age of 40 years, which is a prevalence rising to more than 15% for white women over the age of 80 years, it is estimated that by 2020, the number of individuals in the US with AMD will rise to nearly 3 million individuals.

Several previous genome-wide scans, all of which used small families, had indicated that chromosome 1q31 was one of the several major susceptibility loci for AMD.[5–10] The concordance of these previous studies, which were begun nearly 15 years ago, was remarkable given the different definitions of AMD and approaches used in them. So, these linkage studies provided both the rationale and the focus for the new studies.

The first of the Science studies[3] began with a *de novo* genome-wide scan of more than 116 000 SNPs that used a case–control cohort followed by more intensive, high-density SNP genotyping, whereas the other two studies[1,2] relied upon the earlier linkage studies to focus their search for SNP associations. The work of Hoh and colleagues[3] is only the second published instance of such a genome-wide association study.

Despite the relative small sample sizes and the potential for confounding of ascertainment bias and mismatching of the cases and controls, all three studies found no significant population stratification and reached the same conclusions. Surprisingly, all three groups found comparable levels of risk attributable to the heterozygous and homozygous high-risk 'C' alleles (which have His at position 402 of the CFH protein), as well as similar levels of population-attributable risk of the CFH gene for AMD. Haines and colleagues used families as well as case–controls, while the studies by Edwards and colleagues and Klein and colleagues used only case–control designs. As the studies relied upon case–control designs, which select individuals based on their clinical outcomes and not their exposures, they can only provide odds risk ratios, rather than relative risk values. For a common disease such as AMD, these odds ratios may overestimate the extent to which this gene confers risk for AMD. However, there is no doubt that the polymorphism in the CFH gene is responsible for the linkage signals that have been observed on chromosome 1 and is a significant factor for the pathogenesis of AMD.

In comparison to previous family-based studies, the case–control component of these studies adds a new dimension to the analysis of susceptibility to AMD. In the Edwards *et al* study, the initial AMD group had a family history for 46.7% of cases, while the replicate AMD sample had only an 18.8% positive family history. No information regarding family history of AMD was provided for the case–control groups in the other two studies. However, these case–control studies, which consider AMD cases based on phenotype, irrespective of a family history, provide strong evidence that the contribution to AMD by the high-risk C allele in the CFH gene extends to both familial and sporadic cases. Specifically, they establish that the susceptibility loci identified in AMD families are also relevant to the general population of AMD patients, irrespective of their family history.

These new studies clearly demonstrate the association of the Tyr402His variant in the CFH gene with AMD. However, establishing that the C allele actually causes AMD in individuals who have it is perhaps a more challenging task.[11] Hill[12] provided some of the clearest criteria that can be applied for disease causality and, in this instance, CFH appears to satisfy most of those requirements. In particular, the association is strong, consistent, specific, relatively unbiased, and biologically plausible. In addition, there is evidence of a biological gradient and coherence with previous knowledge, and experimental evidence.

The biological rationale for CFH comes primarily from studies by Hageman and Anderson,[13–16] who have reported the presence of complement factors within the basement membrane and drusen that are typically seen in AMD eyes. There is also ancillary evidence that CFH mutations can lead to Type II glomerulonephritis[17–19] (which is associated with AMD-like changes[20,21]), and that CFH activity is affected by zinc concentration, and is associated with elevated C-reactive protein levels. These ancillary findings provide a rationale for unifying the role of CFH and previous clinical observations, but they are only suggestive at this time.

These studies offer a glimpse of the first gene for AMD that can arguably account

for a significant percentage of the condition (40–50% of the population attributable risk). By contrast, with the exception of the increased relative risk associated with the ε4 allele of ApoE,[22] the majority of studies of AMD that have focused on the genes that have been associated with juvenile forms of hereditary macular degenerations have accounted for a very small percentage of AMD-affected individuals.[23]

The hunt is now on for the rest of the genes that contribute to AMD. However, a word of caution – several editorials have been viewing this new discovery as proof that AMD is the result of an inflammatory process. There is little doubt that the alternate pathway of complement activation is crucial; however, there are likely to be additional, inter-related biological processes that contribute to AMD, and until we identify some of the other contributors to AMD pathogenesis, we can only speculate as to the role of CFH in this disease.

Clearly, future studies are necessary to establish how the polymorphism affects CFH function and to identify the other players in the degenerative process. Additional populations, such as the Icelandic AMD cohort, may have different genes contributing to their disease, especially because they tend to progress towards geographic atrophy as the disease advances, rather than developing choroidal neovascularizations as seen in a high percentage of the individuals in the American studies. The relevance of several of the currently proposed animal models for AMD must be reconsidered. Hopefully, genetic studies will eventually allow for the early detection of at-risk individuals, subsequent estimation of relative risk from these variants, and the initiation of clinical prevention trials with these subjects. We should also be able to begin to develop new animal models that truly are representative of this human disease.

There will remain the rare genetic causes of AMD that can be associated with juvenile macular dystrophy genes, but, regardless, these studies mark a major change in the field in that we are now getting to the heart of the causes of the common form of the disease. It now appears that for this complex disease we no longer face an endless number of rare conditions that defy study or therapy. This discovery demonstrates both the power of genetics and the invaluable contributions of the human genome project and new genotyping technologies to advancing the study of human disease■

Acknowledgements

This study was supported by NEI R01-EY09859, Research to Prevent Blindness, (supported MBG as a Senior Scientific Investigator Award) New York, and The Eye and Ear Foundation of Pittsburgh.

Michael B Gorin is at the Departments of Ophthalmology and Human Genetics, University of Pittsburgh School of Medicine and Graduate School of Public Health, USA.
E-mail: gorinmb@upmc.edu

References

1 Haines JL, Hauser MA, Schmidt S *et al*: Complement factor H varient increases the risk of age-related macular degeneration. *Science* 2005, [E-pub ahead of print].
2 Edwards AO, Ritter III R, Abel KJ, Manning A, Panhuysen C, Farrer LA: Complement factor H polymorphism and age-related macular degeneration. *Science* 2005, [E-pub ahead of print].
3 Klein RJ, Zeiss C, Chew EY *et al*: Complement factor H polymorphism in age-related macular degeneration. *Science* 2005, [E-pub ahead of print].
4 Group TEDPR: Prevalence of Age-Related Macular Degeneration in the United States. *Arch Ophthalmol* 2004; **122**: 564–572.
5 Weeks DE, Conley YP, Mah TS *et al*: A full genome scan for age-related maculopathy. *Hum Mol Genet* 2000; **9**: 1329–1349.
6 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.
7 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.
8 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.
9 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.
10 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.
11 Page GP, George V, Go RC, Page PZ, Allison DB: Are we there yet? Deciding when one has demonstrated specific genetic causation in complex diseases and quantitative traits. *Am J Hum Genet* 2003; **73**: 711–719.
12 Hill A: The environment and disease: association or causation? *Proc R Soc Med* 1965; **58**: 295–300.
13 Mullins RF, Johnson LV, Anderson DH, Hageman GS: Characterization of drusen-associated glycoconjugates. *Ophthalmology* 1997; **104**: 288–294.
14 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. *Progr Retin Eye Res* 2001; **20**: 705–732.
15 Johnson LV, Leitner WP, Staples MK, Anderson DH: Complement activation and inflammatory processes in drusen formation and age related macular degeneration. *Exp Eye Res* 2001; **73**: 887–896.
16 Johnson LV, Ozaki S, Staples MK, Erickson PA, Anderson DH: A potential role for immune complex pathogenesis in Drusen formation. *Exp Eye Res* 2000; **70**: 441–449.
17 Levy M, Halbwachs-Mecarelli L, Gubler MC *et al*: H deficiency in two brothers with atypical dense intramembranous deposit disease. *Kidney Int* 1986; **30**: 949–956.
18 Pickering MC, Cook HT, Warren J *et al*: Uncontrolled C3 activation causes membranoproliferative glomerulonephritis in mice deficient in complement factor H. *Nat Genet* 2002; **31**: 424–428.
19 Hogasen K, Jansen JH, Mollnes TE, Hovdenes J, Harboe M: Hereditary porcine membranoproliferative glomerulonephritis type II is caused by factor H deficiency. *J Clin Invest* 1995; **95**: 1054–1061.
20 Leys A, Vanrenterghem Y, Van DB, Snyers B, Pirson Y, Leys M: Fundus changes in membranoproliferative glomerulonephritis type II. A fluorescein angiographic study of 23 patients. *Graefes Arch Clin Exp Ophthalmol* 1991; **229**: 406–410.
21 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.
22 Schmidt S, Klaver C, Saunders A *et al*: A pooled case–control study of the apolipoprotein E (APOE) gene in age-related maculopathy. *Ophthalmic Genet* 2002; **23**: 209–223.
23 Stone EM, Sheffield VC, Hageman GS: Molecular genetics of age-related macular degeneration. *Hum Mol Genet* 2001; **10**: 2285–2292.