Invited Commentary

At What Age Does Age-Related Macular Degeneration Start?

Adnan H. Khan, PhD; Pirro G. Hysi, PhD; Andrew J. Lotery, MD

Patients presenting to an ophthalmologist with macular drusen at a young age is not an uncommon scenario in medical retina clinics. These young patients want to be informed regarding their future visual prognosis, possible impact on occupation or activities of daily living, and most importantly, any prospect of treatment. What criteria could contribute to an ophthalmologist's confidence in diagnosing early-onset age-related macular degeneration (AMD) as opposed to the early features of an inherited macular dystrophy, such as Doyne retinal dystrophy/Malattia Leventinese or Sorsby fundus dystrophy? In this issue of *JAMA Ophthalmology*, de Breuk et al[1] report the findings of a genotype-phenotype study in patients with early-onset macular drusen. The authors have used the term early-onset drusen maculopathy (EODM) to describe younger (≤55 years) patients with macular drusen and compared 89 patients with EODM with 91 patients diagnosed with AMD who were 65 years or older.

Related article

Strikingly, the study shows that approximately 45% of these patients with EODM developed geographic atrophy or choroidal neovascularization in at least 1 eye by the mean age of 56.4 years, with associated visual impairment. Approximately 30% of patients in the EODM cohort carried a rare complement factor H (*CFH*) genetic variant, compared with approximately 8% of patients with AMD. Patients with EODM tended to carry fewer common variants that are known to predispose to maculopathy in patients with AMD.[2] However, these patients showed a considerable enrichment in genetic risk attributable to rare genetic variation. Rare genetic variants, particularly located in protein-coding regions of genes, tend to have very large effects, inversely proportional with their allele frequency.[3] The presence of rarer risk variants located within the same genes in patients with EODM intriguingly may suggest an explanation for the early onset of symptoms compared with the AMD cohort.

This study demonstrates a shared genetic and phenotypic profile between EOMD and AMD. Therefore, is EOMD a separate disease from AMD or does it suggest that AMD exists in individuals younger than 55 years? The findings described here[1] suggest that patients presenting with an AMD phenotype who are younger than 55 years have a similar genetic basis for the disease, albeit with more rare variants, and as such, have an early-onset form of AMD.

A lower genetic risk score for common AMD genetic risk variants was observed in the EOMD cohort. While the genes involved are the same for both the EOMD and AMD cohorts, the differences in phenotypic expression probably represent a reflection of the genetic architecture, ie, individuals with a certain set of common variations are more likely to express AMD than EOMD.

There are currently 9 ongoing randomized clinical trials targeting the complement system in AMD, including 1 clinical trial (NCT04246866) assessing factor H (FH) supplementation in participants with geographic atrophy and *CFH* variants and another trial (NCT03846193) assessing complement factor I gene supplementation via subretinal gene therapy.[4] In light of the earlier onset of advanced AMD in the EODM cohort, the authors recommend patients with EODM undergoing genetic sequencing of *CFH* for the purpose of genetic counseling and possibly being targeted for future randomized clinical trials of FH supplementation.

To further confirm pathogenicity for these genetic variants, it would also be interesting to measure plasma concentrations of FH and FH-like 1 protein (the latter results from alternative splicing of *CFH* and a shorter isoform of FH) in future studies with EODM. Patients with both a rare *CFH* variant and low FH/FH-like 1 protein levels would seem mechanistically to be the ideal candidates to be targeted for supplementation. Not all genetic variants affect complement protein levels and vice versa; low-complement protein levels can exist for a nongenetic cause. For example, a recent factor I study found the prevalence of complement factor I variants in patients with geographic atrophy with low serum factor I levels was 25%.[5]

This study adds further weight to the suggestion that complement inhibition may be a viable treatment at least in some patients with AMD. However, to date, 1 large randomized clinical trial[6] has shown no benefit of complement inhibition to reduce the rate of geographic atrophy growth, and no other phase 3 clinical trials have shown a benefit of complement inhibition in AMD. Stratifying patients for clinical trials based on genotype may be important. The report by de Breuk et al[1] also suggests including patients younger than the typical age allowed for AMD trials (>55 years) because they are more likely to have genetic variants of large effect size and thus are more likely to respond to a genetic treatment. Importantly, 3 patients within the EODM cohort also had a concurrent diagnosis of C3 glomerulopathy. Ophthalmologists should be aware that complement dysfunction may also cause kidney disease, particularly in younger patients presenting with AMD.

Previous genetic studies have revealed the importance of complement biology in the cause of AMD.[7,8] This work by de Breuk et al[1] builds on this previous work and now suggests we should redefine what age AMD can present at. This may be especially important as we engage in randomized clinical trials of complement inhibition for AMD.

ARTICLE INFORMATION

Author Affiliations: Clinical and Experiment Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom (Khan, Lotery); Southampton Eye Unit, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom (Khan, Lotery); Section of Ophthalmology, School of Life Course Sciences, King's College London, London, United Kingdom (Hysi).

Corresponding Author: Andrew J. Lotery, MD, Clinical and Experimental Sciences, Faculty of

Medicine, University of Southampton, Southampton, United Kingdom (a.j.lotery@soton.ac.uk).

Published Online: October 14, 2021. doi:10.1001/jamaophthalmol.2021.4104

Conflict of Interest Disclosures: Dr Lotery reported personal fees, grants, and stock options from Gyroscope Therapeutics outside the submitted work. No other disclosures were reported.

REFERENCES

1. de Breuk A, Heesterbeek TJ, Bakker B, et al. Evaluating the occurrence of rare variants in the complement factor H gene in patients with early-onset drusen maculopathy. *JAMA Ophthalmol*. Published online October 14, 2021. doi:10.1001/jamaophthalmol.2021.4102

2. Fritsche LG, Igl W, Bailey JN, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48(2):134-143. doi:10.1038/ng.3448

3. Barton AR, Sherman MA, Mukamel RE, Loh PR. Whole-exome imputation within UK Biobank powers rare coding variant association and fine-mapping analyses. *Nat Genet*. 2021;53(8):1260-1269. doi:10.1038/s41588-021-00892-1

4. de Jong S, Gagliardi G, Garanto A, et al. Implications of genetic variation in the complement system in age-related macular degeneration. *Prog Retin Eye Res*. 2021;100952. doi:10.1016/j.preteyeres.2021.100952

5. Khan AH, Sutton J, Cree AJ, et al. Prevalence and phenotype associations of complement factor I mutations in geographic atrophy. *Hum Mutat*. 2021;42(9):1139-1152. doi:10.1002/humu.24242

6. Holz FG, Sadda SR, Busbee B, et al; Chroma and Spectri Study Investigators. Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: Chroma and Spectri phase 3 randomized clinical trials. *JAMA Ophthalmol*. 2018;136(6):666-677. doi:10.1001/jamaophthalmol.2018.1544

7. 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(5720):421-424. doi:10.1126/science.1110189

8. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science*. 2005;308(5720):419-421. doi:10.1126/science.1110359