Aging-Related Macular Degeneration (AMD) is a complex multifactorial disease. Since the first association between a genetic polymorphism and AMD was discovered, the role of genetic factors in the occurrence of AMD is commonly admitted. Smoking and body mass index are important environmental factors associated with an increased risk of AMD, whereas the burden of genetic factors leads to attributable risk estimates up to 60%.

Prediction models based on known genetic and environmental factors associated with AMD recently were established. Seddon and associates described a model showing that the risk of developing exudative AMD in the second eye may vary between 20% and 80% at 3 years, depending on environmental and genetic factors.

The next steps to elucidate the role of genetics in AMD attempt to establish genotype–phenotype correlations, to investigate the genes involved in the natural course and severity of AMD, and to analyze the genes potentially involved in therapeutic responses. It is predictable that genes involved in these diverse steps would differ and that genes involved in the occurrence of AMD would not be the same as genes involved in therapeutic responses.

Genotype–Phenotype Correlations

AMD has a wide range of phenotypes, including occult choroidal neovascularization (CNV), classic CNV, retinal angiomatosis proliferation, and polypoidal vasculopathy for exudative AMD and various rates of progression and shapes of geographic atrophy. Correlations between some genes and phenotypes have been reported. Concerning the early stages of AMD, soft drusen have been linked to the Y402H variant of the complement factor H (CFH) gene. The age-related maculopathy susceptibility protein 2 (ARMS2) genetic risk factor may have an effect that is higher in exudative AMD than in geographic atrophy (odds ratio = 1.37; \( P = 4.2 \times 10^{-7} \)).

Among exudative AMD, classic CNV was found to be more likely to be associated with the ARMS2 gene than with the CFH gene (odds ratio = 2.4; \( P = .18 \)). The Y402H CFH polymorphism revealed some contradictory results for CNV subtypes. Indeed, some studies demonstrated an association with predominantly classic CNV, but other studies demonstrate an association with occult CNV.

More recent studies revealed that the severity of AMD could be associated more specifically with ARMS2. Indeed, earlier age of onset, higher rates of progression, and bilateralism of CNV have been observed with carriers of the at-risk alleles of this gene. In the current article, Tamura and associates confirmed the association of the ARMS2 A69S genotype with second eye involvement of AMD. The authors retrospectively reviewed a series of 326 patients affected with exudative AMD in at least 1 eye by genotyping of ARMS2 A69S. At the initial visit, a risk allele of ARMS2 A69S was seen more frequently in patients with bilateral AMD than in those with unilateral AMD (\( P = .027 \)). Among patients with unilateral CNV at the initial visit, fellow-eye involvement was associated significantly with ARMS2 A69S genotype (hazard ratio, 2.673; \( P = .0013 \)). Among patients with unilateral CNV at baseline, survival analysis revealed that patients with risk homozygous for the high-risk allele had second-eye involvement significantly earlier than those with other genotypes (\( P = .0028 \)).

Pharmacogenetics

The next step of such correlations goes from the degree of response to treatment to therapeutic protocols adjusted to the genotype, the rationale being that the genetic profile of an AMD patient could lead to customized treatment strategies. Concerning prevention of AMD, the use of antioxidants and zinc for prevention of AMD has been correlated with the genetic profile of the patient. Analysis of the Age-Related Eye Disease Studies revealed that the effect of oral supplementation had a significant beneficial effect only on patients without the at-risk allele of CFH, whereas no significant effect was observed in patients carrying the at-risk allele. Prevention of AMD by vitamin and antioxidant supplementation could be considered pointless for patients homozygous for the at-risk allele of the Y402H CFH polymorphism, whereas this preventive approach could be more efficient for patients homozygous for the wild allele of the same single nucleotide polymorphism. Through a similar approach, contradictory results were observed, with a reduced risk of early AMD for homozygotes the high-risk allele of CFH Y402H.
patients with higher dietary intake of zinc, β-carotene, lutein or zeaxanthin, and eicosapentaenoic acid or docosahexaenoic acid.12

Genetic factors that modulate the response to anti-vascular endothelial growth factor therapies currently are difficult to identify. A wide range of therapeutic response is observed, from severe decrease of vision to spectacular improvement of vision. Several factors had been supposed to be associated to therapeutic response, such as the subtype of CNV, environmental factors, tachyphylaxis, or genetic background.13,14 Considering the anti–vascular epithelial growth factor response, it is possible that genes involved in the occurrence of AMD would differ from genes involved in the response to anti–vascular endothelial growth factor treatments. This hypothesis may lead to customized treatments based on genetic profiles. Several other therapeutic approaches are emerging involving different mechanisms, such as vascular endothelial growth factor Trap-Eye. It also could be hypothesized that different genes may modulate the response to different therapeutic targets and exert a different influence on the curative response. This approach has been effective for antineoplastic drugs, cardiovascular drugs, and drugs used for infectious diseases.

Genomics should lead to major developments in the field of AMD through modulation of preventive approaches, customized follow-up of patients, and customized therapeutic approaches by using the genetic profile of each patient. However, prospective studies are needed to validate these concepts and to apply them in the everyday clinical practice.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF Interest and the following were reported. Eric H. Souied has served as a consultant for Novartis, Bayer, and Allergan. Nicolas Leveziel has served as a consultant for Novartis and Allergan. Both authors were involved in Design and conduct of study; Collection and management of the data; Analysis and interpretation of data; and Preparation of the manuscript.

REFERENCES