A Functional Approach to Examine the Role of HTRA1 Versus ARMS2 in AMD

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly. Numerous studies have shown that chromosome 10q26, which surrounds two genes, *HTRA1* and *ARMS2*, represents one of the two strongest genetic loci associated with AMD. *HTRA1* is a multifunctional serine protease that is ubiquitously expressed in mammalian tissues; *ARMS2* is primate-specific with largely unknown function. Nine years have passed since the first publication showing the genetic association of 10q26 with AMD. Scientists still cannot agree on the causal allele at this locus, not to mention the underlying pathophysiological mechanism. This is perhaps the biggest genetic mystery in eye research. This dilemma was reflected in a symposium in ARVO 2014, with a topic on the “Genetics and Pathophysiology of AMD: From SNPs to Disease Modeling.”

In this edition of *IOVS*, Nakayama et al.¹ performed the first animal study to overexpress human *ARMS2* in mice, and to compare the effect of *ARMS2* overexpression versus *HTRA1* overexpression. Two previous studies have shown that overexpressing *HTRA1* in mouse RPE causes defects in the RPE and Bruch's membrane.^{2,3} In the current study, the authors used a different approach by transgenically expressing *HTRA1* globally. They found that *HTRA1* overexpression increases the risk for choroidal neovascularization. This wet AMD phenotype is consistent with previous studies showing that increased *HTRA1* in mouse RPE induces polypoidal choroidal vasculopathy.^{2,4} In contrast, overexpression of neither *ARMS2* nor *ARMS2* (A69S), which corresponds to AMD-associated single nucleotide polymorphism rs10490924, causes any significant phenotype in mice.¹ Considering the controversy surrounding the roles of *HTRA1* versus *ARMS2* in AMD, this study is significant in taking a functional approach to examine their roles in mice. Thus, from a functional perspective, *HTRA1* emerges as a strong candidate for AMD. The key missing puzzle piece is now to show that *HTRA1* level is indeed increased in AMD eyes.

References

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