A Candidate Gene Association Study Identifies DAPL1 as a Female-Specific Susceptibility Locus for Age-Related Macular Degeneration (AMD).

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among white caucasians over the age of 50 years with a prevalence rate expected to increase markedly with an anticipated increase in the life span of the world population. To further expand our knowledge of the genetic architecture of the disease, we pursued a candidate gene approach assessing 25 genes and a total of 109 variants. Of these, synonymous single nucleotide polymorphism (SNP) rs17810398 located in death-associated protein-like 1 (DAPL1) was found to be associated with AMD in a joint analysis of 3,229 cases and 2,835 controls from five studies [combined PADJ = 1.15 × 10(-6), OR 1.332 (1.187-1.496)]. This association was characterized by a highly significant sex difference (Pdiff = 0.0032) in that it was clearly confined to females with genome-wide significance [PADJ = 2.62 × 10(-8), OR 1.541 (1.324-1.796); males: PADJ = 0.382, OR 1.084 (0.905-1.298)]. By targeted
resequencing of risk and non-risk associated haplotypes in the DAPL1 locus, we identified additional potentially functional risk variants, namely a common 897-bp deletion and a SNP predicted to affect a putative binding site of an exonic splicing enhancer. We show that the risk haplotype correlates with a reduced retinal transcript level of two, less frequent, non-canonical DAPL1 isoforms. DAPL1 plays a role in epithelial differentiation and may be involved in apoptotic processes thereby suggesting a possible novel pathway in AMD pathogenesis.