Age-related macular degeneration and functional promoter and coding variants of the apolipoprotein E gene.

Abstract:
Age-related macular degeneration (AMD) is a frequent, multifactorial disease of the central retina and a major cause of irreversible vision loss in industrialized countries. Apolipoprotein E (APOE) has been consistently associated with AMD, particularly its two functional isoforms E2 (predisposing) and E4 (protective). The biological correlate of this association, however, is still unclear. In this study, we have defined an extended haplotype block encompassing the entire APOE gene locus, including known coding as well as cis-regulatory promoter variants. Of the five extended APOE haplotypes common in the general population, two were found to be significantly associated with AMD, namely G-G-G-G-epsilon2 (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.19-2.12) and T-G-A-G-epsilon4 (OR, 0.76; 95% CI, 0.58-0.99). When analyzing common extended haplotype combinations, T-C-G-G-epsilon3/T-G-A-G-epsilon4 exhibited the most prominent effect (OR, 0.32; 95% CI, 0.20-0.51). Intriguingly, we also found one extended epsilon3-haplotype, G-G-G-A-epsilon3, to be protective in the homozygous state (OR, 0.65; 95% CI, 0.49-0.87). Since single nucleotide polymorphism (SNP) rs405509:G>T is a constituent of the extended epsilon-haplotype block and is known to significantly influence APOE promoter activity, we hypothesize that both the relative rate of APOE isoform
expression in conjunction with established functional differences of the respective isoforms may be crucial in mediating AMD pathology. This would also imply that genotyping of the core epsilon-haplotypes alone is not sufficient to estimate AMD risk, but that determination of extended haplotype combinations, including the functional promoter SNP rs405509, is required instead.