Genetic influences on plasma CFH and CFHR1 concentrations and their role in susceptibility to age-related macular degeneration.

Ansari M, McKeigue PM, Skerka C, Hayward C, Rudan I, Vitart V, Polasek O, Armbrecht AM, Yates JR, Vatavuk Z, Bencic G, Kolcic I, Oostra BA, Van Duijn CM, Campbell S, Stanton CM, Huffman J, Shu X, Khan JC, Shahid H, Harding SP, Bishop PN, Deary IJ, Moore AT, Dhillon B, Rudan P, Zipfel PF, Sim RB, Hastie ND, Campbell H, Wright AF (2013) Genetic influences on plasma CFH and CFHR1 concentrations and their role in susceptibility to age-related macular degeneration. *Hum Mol Genet* 22(23), 4857-4869.

Abstract

It is a longstanding puzzle why non-coding variants in the complement factor H (CFH) gene are more strongly associated with age-related macular degeneration (AMD) than functional coding variants that directly influence the alternative complement pathway. The situation is complicated by tight genetic associations across the region, including the adjacent CFH-related genes CFHR3 and CFHR1, which may themselves influence the alternative complement pathway and are contained within a common deletion (CNP147) which is associated with protection against AMD. It is unclear whether this association is mediated through a protective effect of low plasma CFHR1 concentrations, high plasma CFH or both. We examined the triangular relationships of CFH/CFHR3/CFHR1 genotype, plasma CFH or CFHR1 concentrations and AMD susceptibility in

combined case-control (1256 cases, 1020 controls) and cross-sectional population (n = 1004) studies and carried out genome-wide association studies of plasma CFH and CFHR1 concentrations. A non-coding CFH SNP (rs6677604) and the CNP147 deletion were strongly correlated both with each other and with plasma CFH and CFHR1 concentrations. The plasma CFH-raising rs6677604 allele and raised plasma CFH concentration were each associated with AMD protection. In contrast, the protective association of the CNP147 deletion with AMD was not mediated by low plasma CFHR1, since AMD-free controls showed increased plasma CFHR1 compared with cases, but it may be mediated by the association of CNP147 with raised plasma CFH concentration. The results are most consistent with a regulatory locus within a 32 kb region of the CFH gene, with a major effect on plasma CFH concentration and AMD susceptibility.

Beteiligte Forschungseinheiten

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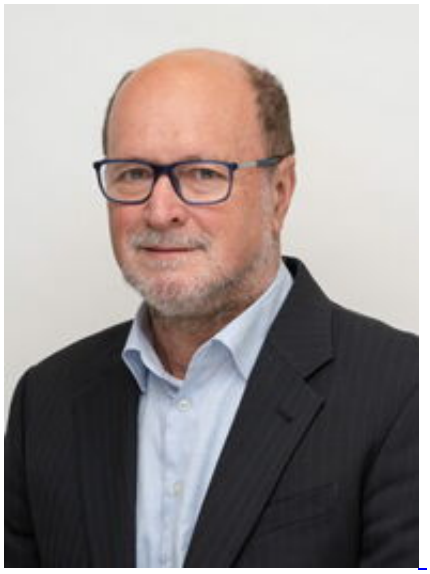
Details



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