Complement factor-H related (CFHR) proteins 1 and 3 and regulation of the alternative pathway activation

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Background: The five CFHR proteins (CFHR1 to -5), together with CFH, comprise a family of structurally related proteins. CFH is a well characterized negative regulator of complement alternative pathway but the biological roles of the CFHR proteins are poorly understood. CFHR proteins contain surface binding domains but lack complement regulatory domains, therefore, a de-regulator function can be suspected for these proteins. A common *CFHR3-1* deletion copy number variation may affect protein expression and complement regulation in this family. Furthermore, homozygous deletion of *CFHR3*- and *1* confers increased risk to the development of autoimmune atypical hemolytic uremic syndrome.
The **aim** of this study was to describe copy number frequencies of CFHR3 and -1 genes in healthy Hungarian population and to link CFHR copy numbers to the activity of complement alternative pathway (AP).
Subjects and Methods: Healthy Hungarian blood donors (119 females, 88 males, mean age 37 years, SD 9.6) were enrolled during regular health-check-up visits in the Kútvölgyi Clinical Center. CFHR3-1 CNVs were determined by multiplex ligation dependent probe amplification (MRC Holland). Activity of the AP was determined by ELISA (LPS induced activation measured by the formation of C9 neo-epitope), whereas complement factor levels measured by immunoturbidimetry (C3), ELISA (C1q, CFH) or radial immune diffusion (C4, CFI, CFB). Anti-Factor H autoantibodies were measured by ELISA.
Results: Heterozygous (2 copies) or homozygous (0 copies) deficiency of *CFHR3*- and *1* was observed in 41.1 and 3.86% of healthy subjects, respectively. Activity of complement AP and levels of C4, C3, CFI, CFB and CFH were similar in the groups of patients with 0, 2 or 4 copies of *CFHR3*- and *1*. Major determinants of AP activity (as identified by multiple regression analysis) were complement factors I, B and C4, and identical models were obtained in the groups of patients with 0, 2 or 4 copies of *CFHR3*- and *1*. Two out of the 207 healthy blood donors were borderline-positive for anti-FH autoantibodies, but did not carry the homozygous deletion of *CFHR3*- and *1*.
Conclusion*:* Based on these observational data we conclude that LPS-induced in vitro activation of complement AP is not affected by deletion of *CFHR3*- and *1*. Further studies better reflecting the in vivo activation of AP are necessary to investigate the potential complement regulatory function of CFHRs.

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