ALZHEIMER RISK ASSOCIATED WITH A COPY NUMBER POLYMORPHISM IN THE COMPLEMENT RECEPTOR 1 INCREASING C3B/C4B BINDING SITES

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Two multicentre, genome-wide association studies (GWAS) provided substantial evidence implicating the complement receptor 1 gene (CR1) in Alzheimer disease (AD) etiology. We performed a follow-up of the GWAS finding in 1883 Belgian patients and control individuals, investigating the effect of SNPs and structural variations in CR1 on AD risk and cerebrospinal fluid (CSF) biomarker levels. We obtained significant association ($p_{\text{adj}}<0.03$ and OR=1.24 (95%CI:1.02-1.51)) for one 130kb risk haplotype containing CR1 almost entirely. Four SNPs in this region correlated with increased Aβ$_{1-42}$ CSF levels in AD patients. Further, we quantified a functional copy number polymorphism (CNP) that results from the presence of low copy repeats (LCRs) in CR1, and produces CR1 protein isoforms that differ in numbers of binding sites for complement components C3b/C4b. We obtained significant association with the common CNP alleles (CR1-F and -S) produced by alterations of LCR1 ($p_{\text{adj}}=0.003$). In an independent group of 2034 French AD patients and control individuals, we showed a trend towards association at the SNP level and significant association with the CR1 CNP ($p_{\text{adj}}=0.038$). Combined analysis confirmed the findings at the SNP ($p=0.002$; OR=1.31, 95%CI:1.11-1.55) and CNP level ($p=0.003$; OR=1.32; 95%CI:1.10-1.59). Our data confirm and extend the GWAS findings and suggest a role for CR1 in Aβ metabolism. Further, quantitative LCR dosage analysis suggested that the AD risk association results from genetic variability in a functional CNP at the CR1 protein level. Individuals carrying an extra CNP copy have a 30% higher risk of developing AD.