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Functional Variant in Complement *C3* Gene Promoter and Genetic Susceptibility to Temporal Lobe Epilepsy and Febrile Seizures

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Abstract

Background: Human mesial temporal lobe epilepsies (MTLE) represent the most frequent form of partial epilepsies and are frequently preceded by febrile seizures (FS) in infancy and early childhood. Genetic associations of several complement genes including its central component *C3* with disorders of the central nervous system, and the existence of C3 dysregulation in the epilepsies and in the MTLE particularly, make it the *C3* gene a good candidate for human MTLE.

Methodology/Principal Findings: A case-control association study of the *C3* gene was performed in a first series of 122 patients with MTLE and 196 controls. Four haplotypes (HAP1 to 4) comprising GF100472, a newly discovered dinucleotide repeat polymorphism [(CA)8 to (CA)15] in the *C3* promoter region showed significant association after Bonferroni correction, in the subgroup of MTLE patients having a personal history of FS (MTLE-FS+). Replication analysis in independent patients and controls confirmed that the rare HAP4 haplotype comprising the minimal length allele of GF100472 [(CA)8], protected against MTLE-FS+. A fifth haplotype (HAP5) with medium-size (CA)11 allele of GF100472 displayed four times higher frequency in controls than in the first cohort of MTLE-FS+ and showed a protective effect against FS through a high statistical significance in an independent population of 97 pure FS. Consistently, (CA)11 allele by its own protected against pure FS in a second group of 148 FS patients. Reporter gene assays showed that GF100472 significantly influenced *C3* promoter activity (the higher the number of repeats, the lower the transcriptional activity). Taken together, the consistent genetic data and the functional analysis presented here indicate that a newly-identified and functional polymorphism in the promoter of the complement *C3* gene might participate in the genetic susceptibility to human MTLE with a history of FS, and to pure FS.

Conclusions/Significance: The present study provides important data suggesting for the first time the involvement of the complement system in the genetic susceptibility to epileptic seizures and to epilepsy.

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