Long-standing balancing selection in the THBS4 gene: influence on sex-specific brain expression and grey matter volumes in Alzheimer’s disease

R. CAGLIANI1, F.R. GUERINI2, F. BAGLIO2, D. FORNI1, C. AGLIARDI2, U. POZZOLI1, S. RIVA1, G.P. COMI3, N. BRESOLIN1, M. CACERES4, M. CLERICI5, M. SIRONI1

1Scientific Institute IRCCS E. Medea, Bosisio Parini (LC), Italy.
2Don C. Gnocchi Foundation ONLUS, IRCCS, Milan
3Dino Ferrari Centre, Department of Physiopathology and Transplantation, University of Milan, Fondazione Ca’ Granda IRCCS Ospedale Maggiore Policlinico, Milan, Italy
4Institut de Biotecnologia i de Biomedicina, Universitat Autònoma de Barcelona, Bellaterra (Barcelona), Spain
5Chair of Immunology, Department of Physiopathology and Transplantation, University of Milan, 20090 Milano, Italy

The THBS4 gene encodes a glycoprotein involved in different processes including inflammation and synaptogenesis. THBS4 is expressed at higher levels in the brain of humans compared to non-human primates, and the protein accumulates in β-amyloid plaques. We analysed THBS4 genetic variability in 4 human populations and show that two major haplotypes (hap1 and hap2) in a region centered around exon 3 are maintained by balancing selection. The two haplotypes have extremely deep coalescence time and modulate THBS4 expression in lymphocytes. Analysis of human brain samples from healthy donors indicated that THBS4 expression increases with age. Analysis of brain expression data in aged healthy individuals showed that variants in the balancing selection region interact with sex in influencing THBS4 expression (p=0.038), with hap1 homozygous females showing the lowest expression level. MRI analysis in 66 Alzheimer’s disease (AD) patients indicated a significant interaction between sex and THBS4 genotype status for peripheral grey matter (p= 0.016) and total grey matter (p=0.031) volumes. Again, the interaction was mainly mediated by hap1 homozygous AD females, in whom the lowest volumes were detected. Because THBS4 is synaptogenic, its brain expression may be up-regulated to counteract the synaptic damage associated with the aging process, and lower expression may result in a more severe degree of pathology in hap1-homozygous AD female patients. Notably, the selection signature associated with THBS4 might not be related to AD, but rather to inflammatory responses, as proposed for other genes involved in AD pathogenesis.