GENETIC VARIATION IN APOE AND NEIGHBOURING GENES IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER’S DISEASE

S. Cervantes1,2, L. Samaranch1, J.M. Vidal1, I. Lamet1, M.J. Bullido3,4, F. Coria4,5, A. Lleó4,6, J. Clarimon4,7, E. Lorenzo1, E. Alonso1, P. Pastor1,2

1Neurogenetics Laboratory, Division of Neurosciences, Center for Applied Medical Research, University of Navarra, 2Department of Neurology, Clínica Universidad de Navarra, University of Navarra, School of Medicine, Pamplona, 3Department of Molecular Biology, Centro de Biología Molecular Severo Ochoa (CSIC-UAM), 4Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, 5Clinic for Nervous System Disorders and Service of Neurology, Hospital Universitario Son Dureta, Palma de Mallorca, 6Neurology Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, 7Neurology Department, Alzheimer’s Laboratory, Neurogenetics Unit, Hospital Santa Creu i Sant Pau, Barcelona, Spain

Introduction: APOE ε4 allele is responsible of 50% of Alzheimer’s disease (AD) risk suggesting that additional genetic risk factors remain unknown.

Aims: We investigated whether, besides APOE ε4, genetic variants in APOE, APOC1, APOC4, APOC2 and TOMM40 genes have an effect in AD risk as well as in the progression from mild cognitive impairment (MCI) to dementia.

Methods: Long-range sequencing of promoter and regulatory regions of such genes in 29 MCI subjects who progressed to dementia revealed seven novel variants. Based on their potential role in transcription regulation and splicing, two of these variants and thirty-four relevant SNPs were genotyped in a large AD/MCI and controls series.

Results: APOE ε4 showed the strongest association with AD risk and reduced age at onset (AAO) in late-onset AD. rs5158 and rs10413089, located in APOC4 and in the 3’ region of APOC2 respectively, increased AD risk independently from APOE ε4 (p= 0.0099 and p=0.011, respectively). APOC1 gene rs4420638, which has a potential role in transcription regulation, had an effect in increasing progression risk from MCI to dementia, although its high LD with APOE ε4 suggested a discrete effect on AD risk. rs157580 at TOMM40 intron 2 increased incidence rate of AD, even after considering only the APOE ε4 noncarriers. rs157580A allele has a potential role in regulation of TOMM40 expression.

Conclusion: These results support the role of additional variants in APOC4, APOC2, and TOMM40 modifying AD risk, AD AOO and MCI progression to AD.