THE CONTRIBUTION OF BIN1 GENETIC VARIABILITY TO ALZHEIMER RISK AND CSF TAU LEVELS IN THE BELGIAN POPULATION

C. Van Cauwenberghe1,2, N. Brouwers1,2, K. Bettens1,2, A. Gil Montoya1,2, S. Engelborghs2,3, R. Vandenberghe4, P.P. De Deyn2,3, K. Sleegers1,2, C. Van Broeckhoven1,2

1Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, University of Antwerp, Antwerpen, Belgium, 2Institute Born-Bunge, University of Antwerp, Antwerpen, Belgium, 3Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerpen, 4Department of Neurology, University Hospitals Leuven and University of Leuven, Campus Gasthuisberg, Leuven, Belgium

Introduction: Recent genome-wide association studies (GWAS) identified the gene encoding bridging integrator 1 (BIN1) as a novel candidate risk gene for late-onset Alzheimer disease (AD). Genetic variants located 5’ upstream of BIN1 were detected with genome-wide significant association. BIN1 is implicated in receptor-mediated endocytosis.

Aim: To fine-map the BIN1 association signal in a Flanders-Belgian AD study group, and to assess the effect of SNP genotypes on cerebrospinal fluid (CSF) biomarker profiles.

Methods: We genotyped 25 SNPs in the BIN1 locus and 35 kb up- and downstream region in 1060 patients and 890 healthy control individuals. CSF levels of beta-amyloid, total tau and phospho-tau were available for 342 patients.

Results: We observed significant genotypic associations for 7 SNPs (p-values ranging from 0.001 to 0.043) of which 2 are located 5’ of BIN1. Strongest evidence of association was observed for a synonymous SNP in exon 6. Interestingly, 5 SNPs correlated with tau levels in CSF of AD patients (p-values ranging from 0.014 to 0.044, of which 3 are located 5’ of BIN1). Of note, the top GWAS SNP, rs744373, is associated with both AD and tau levels in CSF in the Flanders-Belgian study group. No association was found with amyloid and phospho-tau CSF levels.

Conclusion: Our study confirms the GWA association for BIN1 in a Flanders-Belgian study group and extends the observation by showing a correlation with tau levels in CSF, suggesting that BIN1 might affect AD risk through an effect on tau biology.