

A Transcriptome-Wide Association Study of Cognitive Impairment in Subjects With Metabolic Syndrome Adjusted for Adherence to Mediterranean Diet

Oscar Coltell,¹ Carolina Ortega-Azorín,² Eva Asensio,² Eva Pascual,³ Rebeca Fernández-Carrión,² José González,² Javier Guillem-Saiz,⁴ Dolores Corella,² and Rocío Barragán²

¹Universitat Jaume I-University of Valencia-CIBEROBN;

²University of Valencia-CIBEROBN; ³University of Valencia; and ⁴FUNDACION DE LA COMUNIDAD VALENCIANA UNIVERSIDAD INTERNACIONAL DE VALENCIA

Objectives: Mild cognitive impairment has been associated with several genetic and lifestyle factors including diet. However, the number of transcriptome-wide association studies (TWAS) in this field is still very scarce. Our aim was to carry out a TWAS adjusted for adherence to Mediterranean diet (MedDiet) to identify the differentially expressed genes associated with a global cognitive function score, taking diet into account.

Methods: A set of cognitive functions related to cognitive decline was assessed in 103 subjects (aged 64.8 years) with metabolic syndrome. A principal component analysis (PCA) on 5 variables including semantic and verbal fluency, the trail making test (TMT) A and B and the digits total test, was performed to reduce multidimensionality. Only one component with eigenvalues > 1 was identified. This latent variable

had strong direct correlations with semantic and verbal fluency and the digits test, and negative with TMT-A and TMT-B. The standardized score was used as the global cognitive variable representing attention and executive functions. RNA was isolated from leukocytes and after quality control, using the Affymetrix human 20 array, a TWAS was undertaken according to the quality control procedures.

Results: In the TWAS adjusted for sex, age, batch effect, leukocyte types, body mass index, smoking, medications and adherence to MedDiet, we identified several top-ranked differentially expressed genes associated with the global cognitive score, including: HBD3 (Methyl-cpg Binding Domain protein 3) gene ($p = 8.9 \times 10^{-6}$) as the hit, previously associated with neuropathy; GABRP (Gamma-Aminobutyric Acid Type A receptor Pi), involved in the synaptic transmission; and LAG3 (Lymphocyte activating 3), related to neuroinflammation, among others. Moreover, MedDiet was significantly related to the expression of LAG3 gene.

Conclusions: In this TWAS, a composite score for cognitive function is associated with differential expression of several genes related with neurotransmission and neuroinflammation in leukocytes, some of them being additionally modulated by adherence to MedDiet.

Funding Sources: Generalitat Valenciana (grant PROMETEO/2021/021). Grant PID2019-108858RB-I00 is funded by AEI 10.13039/501,100,011,033 and, by “ERDF A way of making Europe”.