



PRINCIPE FELIPE
CENTRO DE INVESTIGACION

CIPF Seminar

Genetic and Epigenetic crosstalk in Alzheimer's disease: towards a more integrative analysis

Speaker: **Dr. Jose V. Sanchez Mut, PhD**

Postdoctoral Researcher, Brain Mind Institute (BMI), École Polytechnique Fédérale de Lausanne (EPFL) CH-1015 Lausanne, Switzerland

Date: **17/05/19- 12:30h**

Place: Saló de Actos CIPF

Abstract: The chances to develop Alzheimer's disease (AD) result from a combination of genetic and non-genetic risk factors, the latter likely mediated by epigenetic mechanisms. In the past, genome-wide association studies (GWAS) have identified an important number of risk loci associated with AD pathology, but a causal relationship thereof remains difficult to establish. In contrast, locus-specific or epigenome-wide association studies (EWAS) have revealed site-specific epigenetic alterations and thereby provide mechanistic insights for a particular risk gene, but often lack the statistical power of GWAS. Combining both approaches, we have found that PM20D1 is a methylation/expression quantitative trait locus (mQTL/eQTL) coupled to an AD-risk associated haplotype, which displays enhancer-like characteristics and contacts the PM20D1 promoter via a haplotype-dependent, CTCF-mediated chromatin loop. PM20D1 is increased following AD-related neurotoxic insults, at symptomatic stages in the APP/PS1 mouse model of AD and in human AD patients, who are carriers of the non-risk haplotype. Furthermore, both genetically increasing PM20D1 expression and pharmacologically mimicking PM20D1 activity reduce AD-related pathologies and improve cognitive performance. In line, PM20D1 genetic reduction aggravates AD-related pathologies. No other genes in the eQTL region show similar effects. These findings suggest (i) that in a particular genetic background, PM20D1 contributes to neuroprotection, (ii) that PM20D1 is compromised in AD-risk haplotype carriers, and (iii) that PM20D1-derived treatments might be suitable therapeutic approaches, from which we expect AD patients, and especially AD-risk haplotype carriers, to benefit in the future.

References:

Sanchez-Mut JV, Heyn H, Silva BA, Dixsaut L, Garcia-Esparcia P, Vidal E, Sayols S, Glauser L, Monteagudo-Sánchez A, Perez-Tur J, Ferrer I, Monk D, Schneider B, Esteller M, Gräff J. PM20D1 quantitative trait locus is associated with Alzheimer's disease. *Nat Med.* 2018. 2018; 24(5):598-603.

Sanchez-Mut JV, Gräff J. Epigenetic Alterations in Alzheimer's disease. *Front. Behav. Neurosci.* 2015; 9 (347).

CON LA FINANCIACIÓN DE:



GENERALITAT
VALENCIANA
Conselleria de Sanitat
Universal i Salut Pública



Fondo Europeo de
Desarrollo Regional
Una manera de hacer Europa
UNIÓN EUROPEA