A transcriptome atlas of FET proteins-regulated genes identifies specific roles in development and differentiation

Shaposhnikov, R. [1] , Zoller, T. [2] , Lombardi S. [1], Nicsanu, R. [1], Graudenzi, A. [3] , Ruepp M.-D. [2] , Luisier, R. [4,5] , Barabino S. [1]

E-mail: roman.shaposhnikov@unimib.it

[1] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy

[2] UK Dementia Research Institute, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[3] Department of Informatics, Systems and Communication of the University of Milan-Bicocca

[4] Department for BioMedical Research, University Bern

[5] SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland

Keywords: Bulk RNAseq, Differential expression, Alternative splicing

Abstract:

Members of the FET protein family (FUS, EWSR1, TAF15) are RNA/DNA-binding proteins involved in mRNA biogenesis and DNA repair, and chromosomal rearrangements or point mutations in these genes are implicated in Ewing sarcomas and neurodegenerative disorders such as amyotrophic lateral sclerosis. Invertebrates and plants contain a single FET protein, whereas the triplication in vertebrates produced three highly conserved paralogs from fish to mammals, suggesting functional specialization. To dissect shared and distinct FET functions in gene regulation, we performed RNA-seq of SH-SY5Y neuroblastoma cells in which each FET gene was individually ablated by genome editing. FET loss caused extensive gene-expression changes and a shared knockout signature of

>500 dysregulated genes. Gene Ontology and gene set enrichment analyses highlighted neuronal development, RNA metabolism and broader transcriptional dysregulation. Each knockout nonetheless showed a specific bias: EWSR1 links FET function to genome stability, FUS combines loss of neuronal/synaptic genes with gain of adhesion–migration genes, and TAF15 represses neuronal and synaptic programmes, revealing a division of labour within the family. Together, these data define a transcriptome atlas of FET-regulated genes in human neuroblastoma cells and show that, while the three FET proteins share broad roles in neuronal gene expression, each also carries distinct regulatory responsibilities.