**MULTI-OMICS CHARACTERIZATION OF NEURODEVELOPMENTAL DISORDERS.**

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The study of neurodevelopmental disorders (NDDs) has been challenging due to the heterogeneity of their genetic etiology and their complex pathophysiology. The use of a multi-omics approaches for the study of these pathologies can provide both insight into their pathophysiology and outline novel therapeutic alternatives.

We performed a targeted metabolomics, lipidomics, and proteomics analyses on CSF samples from 37 patients with alterations in synaptic metabolism and 5 controls. Samples from patients as Rett syndrome, GRINpathies or STXBP1 encephalopathy were included. We performed univariate (UVA) and multivariate statistical analysis (MVA), using Wilcoxon rank-sum test, principal component analysis (PCA), and oPLS-DA. By using the results of both analyses, we identified the biomolecules that were significantly altered and that were important in the separation of the respective groups. On these, we performed pathway- and network-based analyses to define which metabolic pathways were possibly altered in each pathology.

In Rett syndrome samples, we observed alterations in the phenylalanine, tyrosine and tryptophan metabolism pathways, which interestingly depend on the same transporter to cross the blood-brain barrier (BBB). We also observed alterations in the inositol phosphate metabolism and in phosphatidyl inositol signaling. Finally, we detected alterations suggesting dysregulation of the pentose phosphate pathway, which may be a therapeutic target.

Opposite to previous reports, lipidomics analysis showed no significant differences between the controls and the different groups of patients. Notably, we did observe significant differences comparing samples from patients with mutations in *GRIN* vs *STXBP1*, both pathologies with a hypoglutamatergic phenotype. We are currently studying the implication of these alterations in the pathophysiology of both diseases and whether their modulation can constitute a therapeutic target.

Multi-omics integration of complex neurodevelopmental disorders advance the understanding of their pathophysiology, shining light on an under-studied feature as is their metabolic component.