

PI	<i>Matteo Fossati</i>
PROJECT TITLE	Investigating <i>UBE3A</i> -dependent sumoylation imbalance in the pathogenesis of the Angelman syndrome and autism
ABSTRACT	Neurodevelopmental disorders (NDDs) affect millions of individuals worldwide. Given their complex multifactorial origin, the pathogenic mechanisms are largely unknown and no effective therapies are available. This project will focus on the Angelman syndrome (AS) and autism, two NDDs caused by genetic defects of the <i>UBE3A</i> gene, which encodes an E3 ubiquitin ligase. In the brain, ubiquitination regulates multiple pathways and is critical to generate functional neuronal circuits. Emerging evidence indicates that ubiquitination tightly interplays with sumoylation, a ubiquitin-related post-translational modification. Here we will explore the hypothesis that defective ubiquitination caused by <i>UBE3A</i> alterations affects brain sumoylation, contributing to AS and autism pathogenesis. We take a multidisciplinary approach integrating the use of <i>in vivo</i> molecular tools and patient-derived human neurons with proteomics and advanced imaging to characterize alterations of sumoylation in AS and autism.
FUNDING REFERENCE (AMOUNT, STARTING DATE AND DURATION)	Funding: Telethon Research Grant 2020 (GGP20127) Amount: 240.000,00€ Starting date: 01/11/2021 Duration: 3 years
MAIN TECHNICAL APPROACHES TO CARRY OUT THE PRESENT PROJECT	Proteomics, biochemistry, molecular biology, <i>in vivo</i> manipulation of gene function, confocal and super-resolution (STED) microscopy
SCIENTIFIC REFERENCES RELATED TO THE PRESENT PROJECT	Folci A., Mirabella F., Fossati M. Ubiquitin and ubiquitin-like proteins in the critical equilibrium between synapse physiology and intellectual disability. 2020 <i>eNeuro</i> 7 (4): ENEURO.0137-20.2020 Rotaru DC, Mientjes EJ, Elgersma Y. Angelman Syndrome: From Mouse Models to Therapy. 2020 <i>Neuroscience</i> 445:172-189. Vatsa N. and Jana NR. UBE3A and Its Link With Autism. 2019 <i>Front Mol Neurosci</i> . 11: 548 Flotho A. and Melchior F. Sumoylation: a regulatory protein modification in health and disease. 2013 <i>Annu Rev Biochem</i> 82: 357-85