RESEARCH TOPIC MEM25
Investigation of genetic determinants of Angelman syndrome pathophysiology in human neurons

Curriculum MEM

Laboratory name
Cell Biology of the Synapse Lab
Humanitas university

Pre-clinical Supervisor
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Abstract
The Angelman syndrome (AS) is a neurogenetic disorder caused by impaired expression of UBE3A. AS is due to several genetic mechanisms, which are grouped in non-deletions and deletions of 15q11-q13 encompassing UBE3A and other genes. Individuals with deletions have a more severe clinical presentation, indicating that genes flanking UBE3A are important determinants of AS clinical manifestations. The underlying cellular and molecular alterations, and hence the pathophysiology, are largely unknown. Using iPSC-derived human neurons, we will employ CRISPR/Cas9 editing to generate cell lines mimicking the repertoire of AS genetic defects. To evaluate the contribution of 15q11-q13 single genes in AS pathogenesis, cellular and molecular phenotypes will be assessed by means of electrophysiology, morphology and -omics analysis. This project will uncover how genetic hetereogeneity could result in phentypic differences among AS patients and might offer new perspectives for personalized therapies.

Main technical approaches
Molecular and cellular biology, genome editing, optical microscopy, electrophysiology, transcriptomics, proteomics.

Scientific references
Buiting et al. Angelman syndrome — insights into a rare neurogenetic disorder 2016 Nat Rev Neurol

Folci et al. Ubiquitin and Ubiquitin-Like Proteins in the Critical Equilibrium between Synapse Physiology and Intellectual Disability 2021 eNeuro

Frohlic et al. Electrophysiological phenotype in Angelman syndrome differs between genotypes 2019 Biol Psychiatry

Keute et al Angelman syndrome genotypes manifest varying degrees of clinical severity and developmental impairment 2021 Mol Psychiatry

Brief description of the coherence of the project in relation to the PNRR objectives
Coherence with the following PNRR themes: precision and personalized medicine.
Angelman syndrome patients present different clinical manifestations depending on the underlying genetic defects, whose relevance to disease development is not known. This project aims at dissecting the contribution of individual genetic determinants to AS pathophysiology in order to offer tailored therapeutic perspectives to precisely treat AS patients carrying specific genetic alterations.

N. of months abroad
6 months, at VIB Center for Brain and Disease Research, Leuven Brain Institute, at KULeuven, Belgium

Type of contract
PhD scholarship of € 18.000 gross per year awarded by Humanitas University on institutional funds and cofounded with PNRR funds under M.D.M. D.D. N. 118/2023.
This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th August 1984, and is subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent modifications.

Borsa di dottorato pari a € 18.000 annui lordi erogata da Humanitas University su fondi istituzionali e fondi da D.M. 118/2023. Importo non soggetto a tassazione IRPEF a norma dell'art. 4 della L. 13 agosto 1984 n. 476 e soggetto, in materia previdenziale, alle norme di cui all'art. 2, commi 26 e segg., della L. 8 agosto 1995, n. 335 e successive modificazioni.