UNIVERSITÀ DEGLI STUDI DI MILANO

D-MEM PhD-UNIMI | Doctorate program Milan EXPERIMENTAL MEDICINE

Identifying and characterizing novel modifier genes for Rett syndrome

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Rationale and main objectives of this project

In this project we will investigate the role of HPCAL4, a new potential molecular determinant in the pathogenesis of Rett syndrome (RTT), in the attempt to provide new pieces of information to be used for future interventional strategies for this incurable disorder. Rett Syndrome (RTT) is the leading cause of intellectual disability in females due to mutations in the X-linked gene *MEPC2*. Increasing evidence have highlighted main defects in neurons, ranging from neuronal maturation to synaptic transmission. Calcium plays a central role in neuronal signalling related to RTT defects and regulates the activity of a plethora of Ca^{2+}-dependent proteins involved in neuronal functions.
In neurons, a poorly studied Tdark gene called HPCAL4, which belongs to the visinin-like (VSNL) protein family, seems to be involved in the modulation of calcium dynamics even though its precise role is still unknown. Our preliminary data show a clear and robust downregulation of HPCAL4 in RTT indicating its possible involvement in the pathogenesis of this neurodevelopmental disorder. Evidence in literature corroborate our observations and this prompts us to investigate in more details the role of this calcium sensor and its contribution to neuronal function and communication in physiological and pathological contexts. If our experiments will prove that, indeed, this calcium sensor plays a role in the appearance of RTT, then, by studying the mechanisms of action of this protein in healthy neurons and seeing what is wrong in unhealthy ones, we might open new avenues for the development of promising drugs whose activity will have an impact on the severity of Rett symptoms in children, and possibly on other neurological disorders.