

# TITLE OF THE RESEARCH PROJECT: Functional characterization of a novel gene implicated in neurodevelopment

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The advent of NGS techniques has greatly pushed the identification of novel causative genes responsible for rare mendelian disorders. Recently, our group identified recessive mutations in the *FSD1L* (Fibronectin Type III And SPRY Domain Containing 1 Like) gene, encoding for a protein of unknown function expressed in the fetal and adult nervous system, in patients from 3 families who presented developmental delay, intellectual disability, epilepsy, spasticity, and brain malformations (corpus callosum defects, reduced white matter, and mild hydrocephalus). Preliminary studies on patient-derived neural stem cells (NSCs) showed altered ability to migrate and differentiate into neurons and marked dysregulation of several genes encoding for transcription factors and signaling molecules, suggesting a central role for *FSD1L* in neurodevelopment. We also showed that mutant *FSD1L* can alter the centrosome, an organelle essential for cell division and primary cilium function. Aim of this PhD project will be to further dissect the role and related functions of *FSD1L*, using cell lines in which *FSD1L* is silenced or overexpressed and patient-derived cells differentiated towards neuronal lineages.

The first aim will focus on the differentiation of patient and control NSCs and healthy NSCs stably silenced for *FSD1L* to both oligodendrocytes and cortical neurons and their relative functional characterization.

The second aim will focus on the characterization of the role of *FSD1L* at the centrosome during different stages of the cell cycle, and its ability to interact with centrosomal and ciliary proteins through specific domains, employing a healthy primary fibroblast cell line stably silenced for *FSD1L* and constructs lacking selectively each *FSD1L* protein domain.

The results of the project may increase knowledge of regulatory mechanisms of nervous system development, with potential translational impact on other neurodevelopmental diseases.

## Techniques

Cell lines cultures, neural differentiation induction, neural migration assay, immunofluorescence, western blot, cell cycle synchronization and starvation, karyotype analysis, design of deletion constructs, gene overexpression, confocal microscopy, co-immunoprecipitation assay, alpha-LISA assay

