Cell imaging approaches to identify prognostic and predictive biomarkers in Hereditary spastic paraplegias

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Hereditary spastic paraplegias (HSPs) are neurodegenerative diseases caused by several type of mutations, whose clinical manifestations show high inter- and intra- familiar variation. Approximately 45% of these mutations occur in the SPG4 gene, encoding spastin, a microtubule (MT) severing enzyme, that controls cytokinesis, endosomal traffic, lipid droplets (LDs) homeostasis, and axonal transport. To date, no curative therapies are currently available, but approaches based on spastin-enhancing treatments are emerging for HSP-SPG4. So, the challenge for is to identify non-invasive prognostic and predictive HSP-SPG4 biomarkers.

We have developed an automated, simple, rapid, and non-invasive cell imaging-based method to quantify the organization of the MT-cytoskeleton in white blood cells. By using this method, we demonstrated that the parameter “dcnc”, measuring the distance between cell and nucleus centroids, is able to distinguish HSP-SPG4 from healthy donor cells and to sense the effects of spastin-enhancing drugs.

We are now extending our dcnc-based imaging method to a large cohort of SPG4 patient cells to evaluate its sensitivity and specificity in relation with molecular and clinical patient features and to assess the effects of different spastin-elevating drugs. Additionally, we are also focusing on the imaging of other subcellular components affected by spastin mutations, such as LDs.