Giovanni Stevanin*, Christelle Tesson*, Rodrigue Rossignol, Mustafa Salih, Maha Zaki, Rebecca Schule, Filippo Santorelli, Joseph Gleeson, Ali Benomar, Stephan Zuchner, Alexandra Durr*, Alexis Brice*
*Brain an Spine Instiute, Pitié-Salpêtrière Hospital, Paris, France.

New genes in hereditary spastic paraplegias: SPG28 and SPG49

Thanks to extensive collaborations, mainly through the SPATAX network (coordinator: A Durr), we identified loss of function mutations in two functionally related genes (DDHD1 and CYP2U1) in individuals with autosomal recessive forms of hereditary spastic paraplegia (HSP) by using either the classical positional cloning or a combination of whole-genome linkage mapping and next-generation sequencing. The SPG28 (DDHD1) phenotype in 3 families from France, Morroco and Turkey was pure or complex, including neuropathy or cerebellar ocuomotor disturbances. The SPG49 (CYP2U1) phenotype in 5 families from Saudi-Arabia, Egypt, France and Italy ranged from an almost pure and early onset (range : birth to 8) HSP to complex forms involving the upper limbs, mental impairment, neuropathy and dystonia. Interestingly, three subjects with CYP2U1 mutations presented with a thin corpus callosum, white-matter abnormalities, and/or calcification of the basal ganglia. Furthermore, we recently identified a new mutation of *CYP2U1* in a family from Switzerland affecting the first codon but with an asymptomatic carrier aged of 50 years; suggesting an incomplete penetrance or a metabolic compensation in this individual. These genes code for two enzymes involved in fatty-acid metabolism, and we have demonstrated in human cells that the HSP pathophysiology includes alteration of mitochondrial architecture and bioenergetics with increased oxidative stress, and in SPG49, abnormal endoplasmic reticulum structure. Our combined results focus attention on lipid metabolism as a critical HSP pathway with a deleterious impact on critical organelles.