Glucocerebrosidase 2 Deficiency in Hereditary Spastic Paralegia Type SPG46

Rebecca Schüle, Katrien Smets, José Loureiro, Amir Boukhris, Chokhri Mhiri, Emeline Mundwiller, Elodie Martin, Michael Gonzalez, Andrés Caballero Oteyza*, Tine Deconinck, Jean-Jacques Martin, Alexis Brice, Ludger Schöls*, Giovanni Stevanin, Peter de Jonghe, Stephan Züchner*

Center for Neurology and Hertie-Institut for Clinical Brain Research, Tübingen, Germany

In an international collaborative effort we identified mutations in the GBA2 gene to be the cause of autosomal recessive Hereditary Spastic Paraplegia (HSP) Type SPG46. We have identified 10 affected family members from 4 different families. All but one mutation represent likely deleterious changes (nonsense or frameshift mutations), indicating a loss of function disease mechanism. The phenotype of SPG46 is characterized by early onset spastic paraplegia, complicated by cerebellar ataxia, mild to moderate cognitive impairment and cataract in all cases and variably accompanied by axonal neuropathy (70%), bladder disturbances (60%) and mild dorsal column sensory deficits (50%). Hearing loss, Diabetes mellitus and testicular hypotrophy were other complicating features present infrequently. The MRI is characterized by a combined cerebral and cerebellar atrophy, thinning of the corpus callosum and 'hummingbird sign' due to midbrain atrophy at later disease stages.
GBA2 encodes the non-lysosomal glucosylceramidase, that converts glucosylceramide to glucose and ceramide. It is ubiquitously expressed and located at the endoplasmic reticulum as well as the plasma membrane. Whether therapeutic strategies for SPG46 can be transferred from the related disease M. Gaucher, caused by mutations in the lysosomal glucosylceramidase gene GBA1, remains to be studied.