Long-term course and Mutational spectrum of *spatacsin*-linked Spastic Paraplegia

U. Hehr[1], P. Bauer[2], B. Winner[3], R. Schuele[4], G. Uyanik[3], A. Ölmez[5], M. Bonin[2],

H. Topaloglu[5], L. Schoels[4], O. Riess[2], J. Winkler[3]

[1]Department of Human Genetics, University of Regensburg, Germany, [2]Department of Medical Genetics, University of Tuebingen, Germany, [3]Department of Neurology, University of Regensburg, Germany, [4]Research Division for Clinical Neurogenetics, Centre of Neurology and Hertie-Institute for Clinical Brain Research, University of Tuebingen, Germany, [5]Hacettepe University, Department of Pediatric Neurology, Ankara, Turkey

Aims: Hereditary spastic paraplegias (HSPs) comprise a clinically and genetically heterogeneous group of neurodegenerative disorders with progressive spasticity of the lower limbs. We have recently characterized in detail the phenotype of two German pedigrees with AR-HSP with thin corpus callosum (TCC; Winner et al. 2004 and 2006) and could narrow down the SPG11 minimal critical region to a 2.93 cM interval with a maximum LOD score of 11.84 (Oelmez et al., 2006). Recently, KIAA1840 could be identified as the spatacsin gene, associated with SPG11 (Stevanin et al., 2007). We assessed the long-term course and mutational spectrum of SPG11.
Methods: Clinical examination, brain MR imaging and linkage analysis, sequence analysis of 30 candidate genes from the SPG11 locus.
Results: Spastic paraplegia in patients with spatacsin mutations (n=20) developed during the second decade of life. The spastic paraplegia rating scale (SPRS) revealed severely compromised walking between the second and third decade of life (mean SPRS score >30). Impaired cognitive function was associated with a severe atrophy of the frontoparietal cortex, TCC and bilateral periventricular white matter lesions. Progressive cortical and thalamic hypometabolism in the FDG-PET was observed. Sural nerve biopsy showed a loss of unmyelinated nerve fibers and accumulation of intraaxonal pleomorphic membranous material. Mutational analysis of spatacsin revealed 6 novel and one previously reported frameshift mutation, two novel nonsense mutations and the first two splice mutations to be associated with SPG11.
Conclusions: We demonstrate that not only frameshift and nonsense mutations, but also splice mutations result in SPG11. Mutations are distributed throughout the spatacsin gene and emerge as major cause for ARHSP with TCC associated with severe motor and cognitive impairment. The clinical phenotype and the ultrastructural analysis imply a disturbed axonal transport of long projecting neurons.