Neurodevelopment defects in SPG11

Mutations in the spastic paraplegia gene 11 (SPG11), encoding spatacsin, cause the most frequent form of autosomal-recessive complex hereditary spastic paraplegia (HSP) and juvenile-onset amyotrophic lateral sclerosis (ALS5). When SPG11 is mutated, patients frequently present with spastic paraparesis, a thin corpus callosum, and cognitive impairment. We previously delineated a neurodegenerative phenotype in neurons of these patients. Our current analysis recapitulates early developmental phenotypes of SPG11 and outlined their cellular and molecular mechanisms in patient-specific induced pluripotent stem cell (iPSC)-derived cortical neural progenitor cells (NPCs). We generated and characterized iPSC-derived NPCs and neurons from 3 SPG11 patients and 2 age- matched controls. Gene expression profiling of SPG11-NPCs revealed widespread transcriptional alterations in neurodevelop- mental pathways. These include changes in cell-cycle, neurogenesis, cortical development pathways, in addition to autophagic deficits. More important, the GSK3ß-signaling pathway was found to be dysregulated in SPG11-NPCs. Impaired proliferation of SPG11-NPCs resulted in a significant diminution in the number of neural cells. The decrease in mitotically active SPG11-NPCs was rescued by GSK3 modulation. This iPSC-derived NPC model provides the first evidence for an early neurodevelopmental phenotype in SPG11, with GSK3ß as a potential novel target to reverse the disease phenotype.

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Prof. Dr. Beate Winner
IZKF N3
FAU Erlangen-Nürnberg
Glückstr. 6
91054 Erlangen
T: +49-9131-85-39301
Beate.winner@fau.de