Neurofibromatosis type I: insertion of a stopcodon in exon 9a

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Neurofibromatosis type I is one of the most common single gene disorders (prevalence = 1:3500), that affects the central nervous system, and can cause learning problems in 30-60% of the patients. Mutations in the NF1 gene (located on chromosome 17q11.2) can give rise to many different phenotypes, without a correlation between phenotype and genotype. We are interested in how Nf1 contributes to learning and memory.
The Nf1 gene encodes for neurofibromin, which is known to act as a Ras GTPase, causing inactivation of Ras. Presynaptically, Ras is involved in the phosphorylation of synapsinI. SynapsinI binds vesicles to the cytoskeleton. Phosphorylation of synapsinI leads to disconnection of the neurotransmitter-vesicles from actin and transport to the active site of the synapse. A mutation in the NF1 gene causes increased levels of active Ras, leading to increased phosphorylation of synapsinI, and increased release of neurotransmitter. It has been shown in mouse models that a mutation in the NF1 gene predominantly affects the inhibitory neurons (Costa et al, 2002).
Recently an alternative spliced form of the NF1 gene has been found, containing exon 9a. This exon 9a seems to be expressed exclusively in the central nervous system, and even more: exclusively in neurons! The amount of expression also differs per region in the brain (60-70% in hippocampus and cortex, 10-15% in cerebellum). A mouse-model is generated with a stopcodon inserted in exon 9a. Molecular analysis showed no changes on protein level or quantitative RNA level, although the rt-PCR did show absence of exon 9a. Thus the insertion of a stopcodon most likely causes skipping of the exon, a mechanism that also has been observed in Nf1 patients (Messiaen et al, 2000). We are currently analyzing the behavioral phenotype of this model, to see whether this isoform has a role in learning and memory.

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