Assessment of prion-like behavior of pathologic protein aggregates from ALS patients
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Research question and background
This project will assess, if aggregates of TAR DNA-binding protein (TDP-43) from brains of patients with amyotrophic lateral sclerosis (ALS) behave in a prion-like manner. The aim of our study is to better understand pathologic mechanisms in ALS, which are only poorly understood. The results of our study may lead to novel treatment options for ALS patients. ALS pathology is associated with the formation of TDP-43 aggregates. Because neuronal involvement in ALS progresses in a similar sequence in different patients it has been suggested that abnormal proteins in ALS may propagate in a prion-like manner (Braak et al., 2013; Brettschneider et al., 2013). It has been suggested that the spreading manner is consistent with the induction and dissemination of TDP-43 pathology from the cortical neuronal projections, via axonal transport, through synaptic contact to the spinal cord and other regions of the brain. Prion-like spreading in a mouse model for synucleopathies has also been shown for α-synuclein aggregates from post-mortem tissues of patients with multiple system atrophy (Watts et al., 2013).

Methods and tissues used
Post-mortem tissue from patients containing TDP-43 aggregates have been processed to give 1% tissue homogenates in phosphate buffered saline. Two cohorts of 12 transgenic mice expressing human TDP-43 have been inoculated intracerebrally with 30 µl of the respective patient tissue homogenate. Control mice have been inoculated with phosphate buffered saline. The Tg(TDP-43) mice that we use in our experiments express human TDP-43 but normally do not develop any pathology throughout their life. After inoculation the neurologic status of the mice is being monitored to assess if and when these mice will develop disease. Once the mice develop disease or after 500 days after inoculation, the animals will be sacrificed to biochemically and immunohistochemically assess the potential spread of pathologic TDP-43 aggregates.

Results and conclusion
This study is ongoing and no results or conclusions have been obtained yet.

References