# PAPER OF THE MONTH 04/2023

TRR 295 ReTune

## Peripheral nerve injury elicits microstructural and neurochemical changes in the striatum and substantia nigra of a DYT-TOR1A mouse model with dystonia-like movements.

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Basic science has made important strides in understanding the pathomechanisms behind dystonia, however, it has been hampered by a lack of rodent models with both construct and face validity. Most transgenic mouse models for DYT-TOR1A dystonia, the most common monogenic form of dystonia, have failed to show a dystonic phenotype. In order to fill this gap, we present an in-depth study of a new symptomatic mouse model for DYT-TOR1A dystonia. The mouse model is based on the second-hit hypothesis, which postulates an interplay of genetic predisposition and extragenetic factors in dystonia symptomatogenesis. The hypothesis proposes that environmental factors disturb a barely compensated, structurally and neurochemically altered sensorimotor system. It is well known that genotype does not predict phenotype in dystonia, penetrance for DYT-TOR1A is low with 30%. Herein, dystonia-like movements were triggered in a genetically predisposed hΔGAG3 mouse model, which overexpresses the human mutated TOR1A gene, via the application of a peripheral trauma. In order to evaluate the triggered phenotype, we present for the first time a deep-learning based kinematic analysis of dystonia-like movements of the hindlimbs. Using DeepLabCut for a markerless pose estimation, we developed a dedicated software for the automated identification of dystonia-like movements. We were able to show that hΔGAG3 mice develop lasting dystonia-like movements after nerve crush compared to naïve hΔGAG3 mice and wildtype control mice.

We focused on the basal ganglia for the identification of genotype- and phenotype-dependent changes. Tracing of striatal medium spiny neurons revealed endophenotypical abnormalities in hΔGAG3 mice in form of reduced and shortened dendrites with a reduced number of spines. The evaluation of the number and volume of striatal interneurons showed that the nerve crush causes changes in parvalbumin+, ChAT+ and nNOS+ interneurons independent of the genotype, revealing the extensive central changes that can accompany a peripheral trauma even in the healthy brain. Calretinin+ interneurons showed genotype-dependent abnormalities. Seminal findings further include a highly significant hypertrophy of dopaminergic neurons in the hΔGAG3 mice showing dystonia-like movements compared to all other groups. Potentially linked to it, we were able to show significantly elevated dopaminergic levels in the striatum of hΔGAG3 mice post nerve crush compared to all other groups.

This publication highlights the importance of extragenetic factors in the symptomatogenesis of DYT-TOR1A. This new, symptomatic mouse model allows for differentiation between genotype- and phenotype-induced abnormalities. We were able to corroborate the suspected involvement of the dopaminergic system in DYT-TOR1A dystonia, especially its connection to the manifestation of dystonic movements in mutation carriers.

**Dr. med. Lisa Rauschenberger**

Lisa Rauschenberger is a resident in the neurology department at the University hospital of Würzburg with a focus on movement disorders. Within this field, her research work focuses on unraveling the impact of environmental factors on the pathophysiology of Parkinson's disease and dystonia at the hands of rodent models.

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Chi Wang Ip is the Vice Chairman of the Neurology department at the Universitätsklinikum Würzburg. His research is focused on understanding the molecular, cellular and network mechanisms underlying movement disorders and utilizing this understanding to develop novel treatment strategies to improve patient outcomes..

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