

Towards the understanding of pathological protein processing and toxicity in Machado-Joseph disease.

<https://www.neurodegenerationresearch.eu/survey/towards-the-understanding-of-pathological-protein-processing-and-toxicity-in-machado-joseph-disease/>

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Netherlands

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Towards the understanding of pathological protein processing and toxicity in Machado-Joseph disease.

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Research Abstract

Machado-Joseph Disease (MJD, syn. spinocerebellar ataxia type 3; SCA3) is an autosomal dominantly inherited neurodegenerative disorder caused by expansion of polyglutamine(polyQ)-encoding CAG repeats in the MJD1 gene. Neuronal nuclear inclusions (NNI)containing the gene product ataxin-3 (ATXN3) are a hallmark of MJD.

Compelling evidence indicates that the proteolytic cleavage of ATXN3 leads to the formation of misfolded intermediates, which eventually accumulate to form NNIs. However, the exact mechanism of how mutated ATXN3 is processed in the cell, how this mostly cytoplasmatic protein is shuffled to the nucleus, which other genetic predisposition factors determine disease severity and the exact relationship ATXN3 aggregation and toxicity remains elusive. We will combine latest cell culture techniques with state-of-the-art biochemical studies, neurogenetics, imaging and animal models. Specifically, we will identify candidates of genetic modifiers by deep sequencing in a cohort of MJD patients. Special emphasis in our studies will lie on the subcellular localization of ATXN3 related to toxicity and the autophagy degradation pathway. Induced pluripotent stem cells (iPSC) will serve as a new in vitro model to study cleavage, aggregation, processing, stress and toxicity directly in human neurons. Applying high-resolution live-cell imaging will facilitate real-time assessment of aggregation and proteotoxicity. We expect this consortium to generate fundamental new insight into the pathology of MJD in a highly innovative and complementary fashion.

Further information available at:

<http://www.zonmw.nl/nl/projecten/project-detail/towards-the-understanding-of-pathological-protein-processing-and-toxicity-in-machado-joseph-disease/samenvatting/>

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