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

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

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ZonMw

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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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