



## LECTURE

# Models of disease: *C. elegans*

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### Abstract

*Caenorhabditis elegans* has been successfully used to model neurodegeneration *in vivo*, mainly due to the conservation of basic cellular mechanisms such as neuronal signaling, cell death/survival, proteostasis and aging. Despite having relatively few neurons, *C. elegans* exhibit complex behaviors that can be assayed to monitor neuronal dysfunction, which can be combined with biophysical assays to examine protein aggregation in live neurons of interest. Here, we describe how the use of a *C. elegans* model of Machado-Joseph disease (MJD) pathogenesis allowed the identification of novel genetic modifiers of disease and promising cellular targets for

therapeutical intervention. Pan-neuronal expression of mutant ATXN3 led to a polyQ-length dependent, neuron subtype-specific aggregation and neuronal dysfunction. Wild-type ATXN3 is irreversibly recruited into polyQ-containing cellular aggregates, aggravating the animals' motor dysfunction. Aging influenced the ATXN3 phenotypes which can be suppressed by lifespan increasing mutations in *C. elegans*. A drug repurposing screen identified pharmacological modulators of neurotransmission as potential treatment for MJD. Chemical genetics and validation in higher organisms will help to shed light into its mode-of- action in MJD.

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