

## **A transgenic zebrafish model of Machado-Joseph disease to test potential disease treatments**

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Machado Joseph disease (MJD), also known as spinocerebellar ataxia-3 (SCA3) is a hereditary neurodegenerative disease that affects muscle control and coordination. The disease is caused by an extended trinucleotide repeat region (CAG) in the gene ATXN3/MJD1, encoding a polyglutamine (polyQ) region within the ataxin-3 protein. Whilst the wild-type (WT) ataxin-3 protein contains 12-44 glutamine residues, as many as ninety glutamines are found in the ataxin-3 protein of MJD patients. We have successfully established the first transgenic zebrafish model of MJD. These zebrafish express human ataxin-3 containing either 19Q (WT) or 84Q (MJD). Immunoblot analysis of protein lysates extracted from our transgenic SCA-3 zebrafish revealed the presence of ataxin-3 cleavage products similar to those found in MJD patient samples. These fragments were present at all ages examined from three days post fertilization (dpf) through to 12 months old. We identified a marked motor phenotype developed in ataxin-3-84Q zebrafish from 4 months old, with ataxin-3-84Q zebrafish swimming slower than ataxin-3-19Q fish. A more sensitive behavioural test (escape response during darkness) detected reduced swimming speeds in ataxin-84Q zebrafish than ataxin-19Q as early as 6dpf. This motor phenotype provides a useful readout for drug screening assays because it is easily quantified and occurs at an age that zebrafish larva can be treated in small multi-well plates. Our results indicate that our transgenic zebrafish model of MJD is relevant to the human disease and will be a valuable tool for testing potential disease treatments.