**Exploring cognitive phenotypes and extra-cerebellar pathology in a murine model of MJD**

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**ABSTRACT:**

Machado Joseph disease (MJD, also known as spinocerebellar ataxia type-3) is a fatal form of hereditary ataxia, characterised by progressive motor impairments and widespread degeneration throughout the central nervous system, including the cerebellum. Historically, the cerebellum has been appreciated for its role in motor functions, however emerging evidence suggests that the cerebellum may also play an important role in cognitive behaviours and emotion. Changing perceptions of the cerebellum have also led to wider recognition of non-motor symptoms in patients with diseases affecting the cerebellum, such as MJD and other forms of spinocerebellar ataxia. It is now widely reported that patients with forms of spinocerebellar ataxia also develop anxiety and depression, however it is questioned whether this is a direct consequence of the inherited genetic mutation. Previous investigations of anxiety-like behaviour in murine models of MJD have produced conflicting findings. The primary aim of this study was to determine whether transgenic CMVMJD135 mice recapitulate the anxiety phenotypes observed in MJD patient cohorts and to investigate which area of the brain may be driving anxiety-like behaviour. First, we demonstrate that whilst both male and female CMVMJD135 mice develop motor impairments, male MJD mice develop motor impairments earlier, displaying a more severe motor phenotype. We report that male MJD mice also display increased anxiety-like behaviour, exhibiting thigmotaxis behaviour within the open field and decreased exploration of the open arms within the elevated plus maze. In contrast, female MJD mice behave similarly to wildtype mice and do not display anxiety-like behaviour. This finding of anxiety-like behaviour exclusively in male MJD mice is interesting, as both sexes ubiquitously express mutant human *ATXN3* and develop ataxin-3 protein aggregates within the cerebellum and amygdala. Further, both male and female MJD mice failed to discriminate between the novel and familiar object in the novel object recognition task, suggesting possible alterations to hippocampal function and memory impairments. Future studies should aim to further elucidate the possible disease mechanism or pathological changes within the MJD brain that could be driving the observed behavioural changes.