**Investigating potential causes of altered gut microbiome in Machado-Joseph disease mice**

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**ABSTRACT:**

Machado-Joseph disease (MJD) is caused by the inheritance of an expanded trinucleotide repeat region within the *ATXN3* gene, leading to an expanded polyglutamine (polyQ) tract within the ataxin-3 protein. PolyQ-expanded ataxin-3 protein is highly aggregation prone, and its presence leads to neurodegeneration within the brain and spinal cord.

Growing evidence suggests that changes to gut microbiome may occur in neurodegenerative diseases. Indeed, previous work by our team has identified that alterations to the composition of gut microbiome occur in the CMVMJD135 mouse model of MJD, even prior to the onset of motor symptoms. Here, we aimed to explore the possible mechanisms causing these changes within the microbiome-gut-brain axis, and whether these changes preceded or followed central neurodegeneration. We found that male MJD mice had significantly different microbiome communities even at just 5-weeks-old, and that ataxin-3 protein aggregates were also present in their brains at these ages. In contrast, we did not observe any changes to gut morphology, enteric neuron number or presence of protein aggregates within enteric neurons. Finally, we report that male MJD mice have faster total gut transit times than wild-type controls from 9 weeks of age, and explore potential triggers of this functional change. Together, these findings demonstrate that gut dysfunction and microbiota changes do occur in this mouse model of MJD, prior to onset of motor impairment, and warrants further investigation.