Missing Piece of the Puzzle: Characterizing GI Motility in CLN1 Disease

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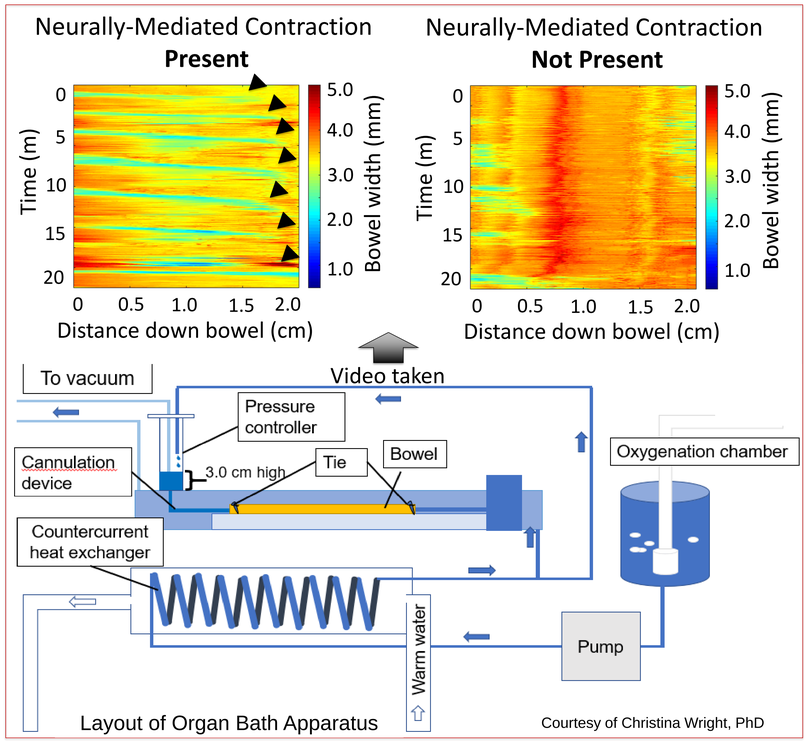
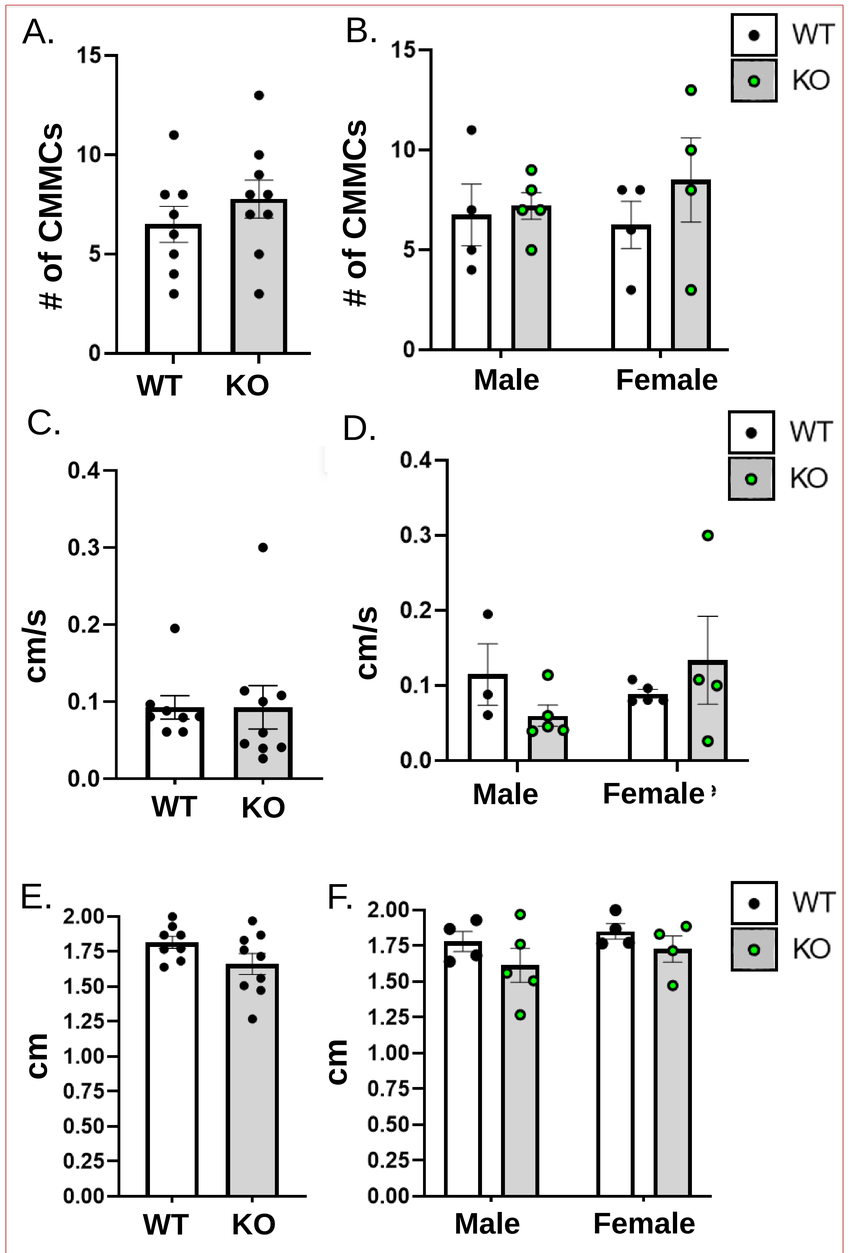
Abstract

CLN1 disease is a fatal pediatric neurodegenerative disorder caused by autosomal recessive loss-of function mutations in the *PPT1* gene. *PPT1* encodes lysosomal enzyme palmitoyl protein thioesterase-1 (PPT1). PPT1 deficiency causes build-up of storage material in many cell populations, but for unknown reasons leads to particular devastation in the central nervous system (CNS). Previous therapeutic approaches in *Ppt1-/-* mice used AAV-mediated gene therapy to the brain and spinal cord to replace the missing enzyme. While this strategy significantly improved survival, *Ppt1-/-* mice still died prematurely. New preliminary data suggest CLN1 disease also causes profound pathological changes in the enteric nervous system (ENS) and bowel motility abnormalities. Gut dysfunction is also common in children with CLN1 disease. Here we characterize and measure *ex vivo* neurogenic motility patterns in the colon and distal small bowel of *Ppt1-/-* mice at an advanced disease stage using an organ bath apparatus. Our data provide evidence supporting the presence of region-specific motility defects in *Ppt1-/-* mice. These data also propose sex-dependent differences in the motility phenotype at the disease-stage analyzed, suggesting a sex-dependent difference in disease progression outside the brain and spinal cord.

Methods

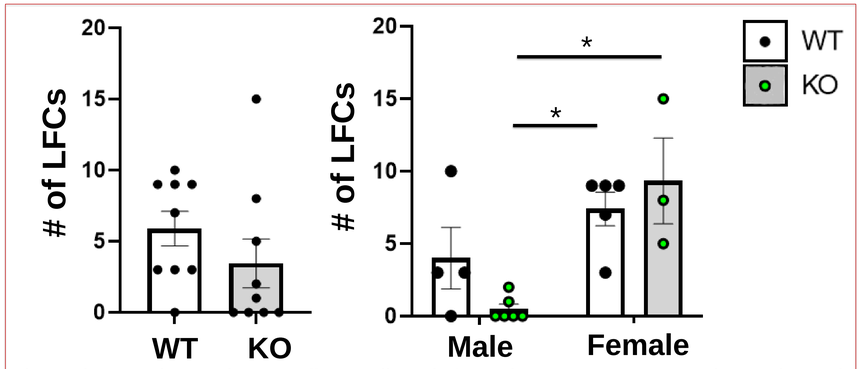


Ppt1-/- mice do not have abnormal colonic motility



(A, B) Number of neurally-mediated colonic migrating motor complexes (CMMCs) occurring in 20 minutes. (C, D) CMMC rate traveling distally down the bowel. (E, F) Average distance traveled (in cm) of each CMMC. All data passed normality (Shapiro-Wilks Test). Significance tested using Student's T-Test (genotype) and Two-Way ANOVA (genotype and sex effects).

Ppt1-/- mice have abnormal distal small bowel motility



(A, B) Number of neurally-mediated low frequency contractions (LFCs) occurring in 20 minutes. Data did not pass normality (Kolmogorov-Smirnov test). Significance tested using Mann-Whitney (genotype) and Chi Square Test (genotype and sex effects). Sex:genotype interaction (P=0.03).

Discussion and Next Steps

This study is the first to assess ENS involvement in pediatric lysosomal storage disease. Our findings are novel in three ways:

1) Our findings represent the first reported motility defect in an animal model of CLN1 disease.
2) Our findings suggest that disease progression in the enteric nervous system is sex-dependent.
3) Our findings demonstrate region specific motility defects.

Next Steps:

- Increase the number of mice evaluated.
- Evaluate the ability of ENS-directed gene therapy to return normal contractile patterns.

References

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