Title
Translational Behavioral Assessment of the E200KPathogenic Variant of the B56δ-subunit of the ProteinPhosphatase 2A (PP2A) that Results in Jordan’s Syndrome

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Translational Behavioral Assessment of the E200K Pathogenic Variant of the B56δ-subunit of the Protein Phosphatase 2A (PP2A) that Results in Jordan's Syndrome

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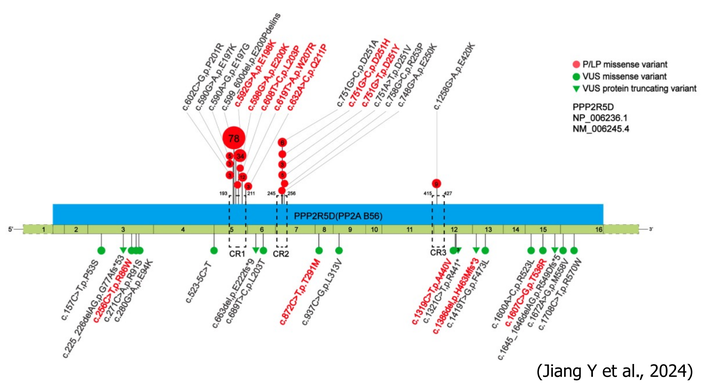
Introduction

- Protein phosphatase 2A (PP2A) is a family of multi-subunit enzymes essential for the regulation of many functions such as gene transcription, cell division, and growth. (Eichhorn et al., 2009)
- A few different pathogenic missense variants in PPP2R5D, the B56δ-subunit of protein phosphatase 2A, cause Jordan's Syndrome. The most common of these variants are E198K, E200K, and E420K.



(Jiang Y et al., 2024)

- Clinical severity varies depending on the inherited pathogenic variant, with increasing severity in the following order: E200K, E198K, and E420K.
- Clinical characterizations of individuals with Jordan's Syndrome include global developmental delays, seizures, macrocephaly, hypotonia (lacking muscle tone), inattention, social and sensory challenges often associated with autism, and disruptions in sleep. (Levine and Chung, 2023)
- There are no approved pharmaceutical therapies for treating Jordan's Syndrome, and no biological (genome-editing) precision medicine tools in development.

Hypothesis

We hypothesize that distinct, translationally relevant phenotypes will be quantifiable in each pathogenic mouse model of Jordan's Syndrome and that the severity of these phenotypes will be correlated with specific genetic variants.

Objective

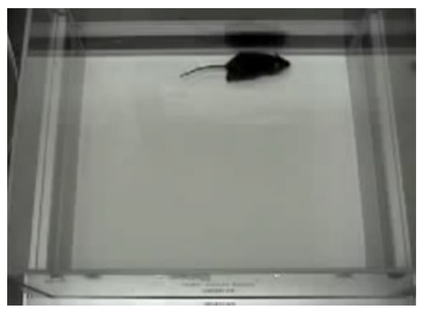
To discover behavior and translational phenotypes in Jordan's Syndrome mouse models, providing a robust *in vivo* model system for testing innovative therapeutics for individuals affected by Jordan's Syndrome.

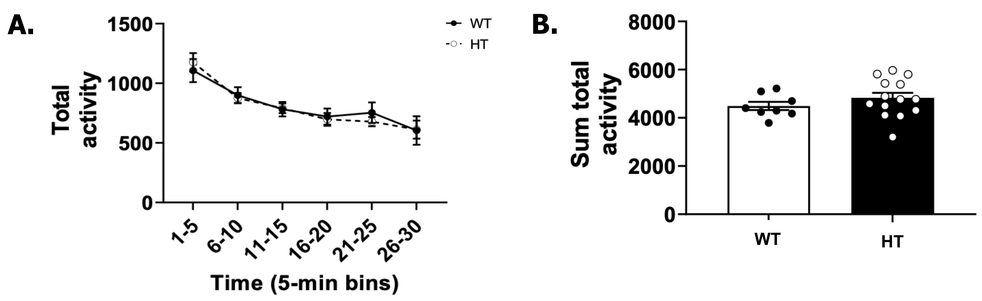
Methods

- Cohort 1: N= 12 WT and 12 HT
  - Motor: Open field, Y-maze
  - Learning and Memory: Novel object recognition
- Cohort 2: N= 9 WT and 14 HT
  - Motor: Open field, Y-maze
  - EEG (spiking analysis + rapamycin therapy)

Results

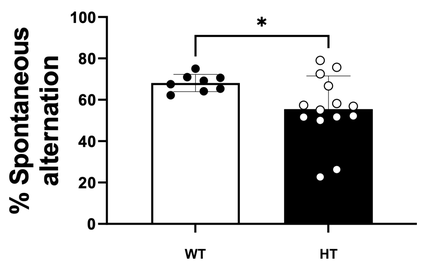
Fig. 1: Motor Exploration – E200K





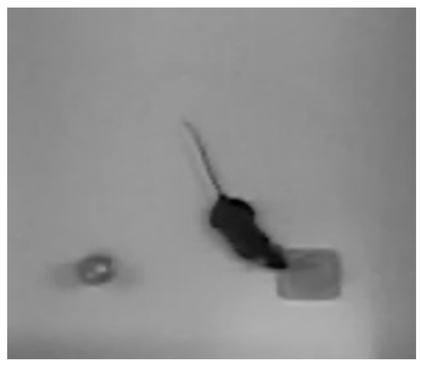
Motor Exploration in the open field was the same between WT and HT animals (A, B).

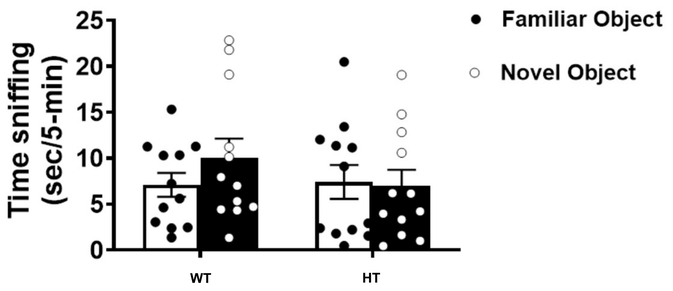
Fig. 2: Spontaneous Alternation Behavior (Y-Maze) – E200K



Spontaneous alternation behavior in the Y-maze was decreased in HT animals compared to WT animals.

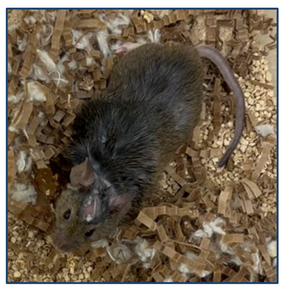
Fig. 3: Novel Object Recognition (NOR) Memory – E200K



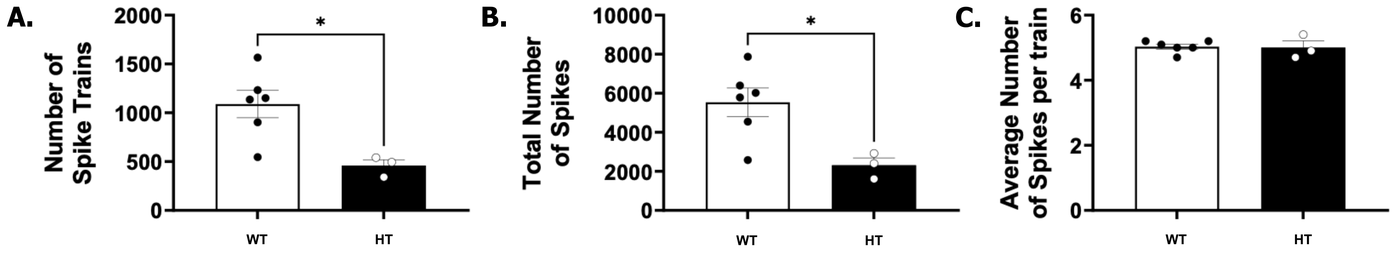


During NOR testing HT mice had no increase in novelty exploration.

Fig. 4: EEG Spiking Analysis – E200K



During EEG recording, HT animals were noted to have a smaller number of spike trains (A) and a decreased total number of spikes (B) compared to WT animals. There was no difference in the average number of spikes per train between groups (C).



Conclusions

Our studies using the E200K mouse model showed no impact on motor exploration, a decrease in learning and memory, and reduced spiking activity.

Future Directions

- We will repeat these experiments in the E198K and E420K variants to directly compare the differences in clinical severity between them.
- Therapeutic studies are ongoing, including gene-editing and repurposed pharmaceuticals.

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