

Piezo2 GOF Mutations Reduce Muscular Response to Stretch in an Age-dependent Manner

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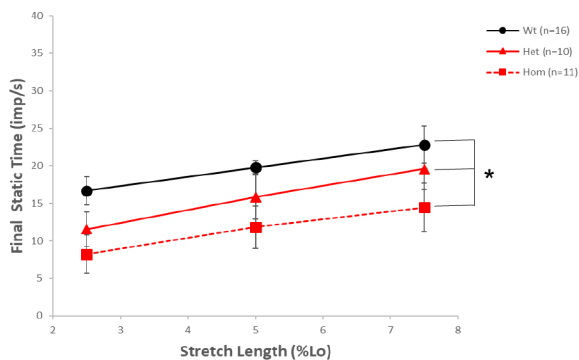
Introduction

- Proprioception is the sense of body position in space, and is required to coordinate fine motor movement.
- Information about muscle stretch is conveyed through changes in the firing frequency of action potentials reported by muscle spindle afferents (MSAs).
- Piezo2 is a mechanosensitive cation channel found in MSAs that opens in response to stretch. Prior research found that MSAs lacking Piezo2 do not respond to stretch, indicating that Piezo2 is necessary for mechanotransduction in MSAs.
- Preliminary data suggests that adult mice with a Piezo2 gain of function (GOF) mutation that is observed in the human disease distal arthrogryposis type 5 (DAG5) exhibit a decreased response to stretch, despite Piezo2 being more likely to open. This is potentially due to developmental compensation.
- **We hypothesized that P7-11 day old mice with the Piezo2 GOF will exhibit an increased response to stretch when compared to wildtype mice.**

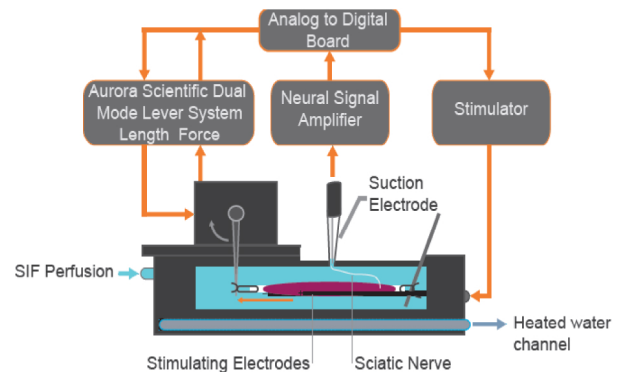
Methods

- For each mouse, the Extensor Digitorum Longus (EDL) muscle and sciatic nerve were isolated in an oxygenated Synthetic Interstitial Fluid (SIF) bath.
- Extracellular electrical recordings were taken from the sciatic nerve.
- Muscles were held at the optimal resting length (L0) and were stretched to 2.5%, 5.0%, and 7.5% above L0 for 4 seconds.
- The firing frequency of action potentials during the Final Static Time (FST), 3.25-3.75 seconds after the start of the stretch, was compared.
- Recordings were taken from the following mice:
 - Adults (2-4 months old): 11 GOF homozygotes, 10 GOF heterozygotes, and 16 WT
 - Baby (7-11 days old): 4 GOF homozygous, 7 GOF heterozygous, and 7 WT

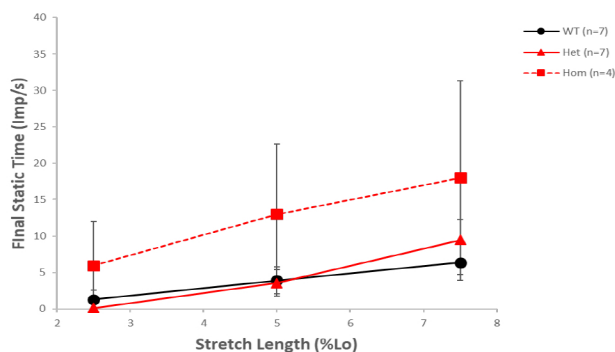
Adults with the Piezo2 GOF are less sensitive to stretch



Experimental Setup



Young mice with the Piezo2 GOF have similar stretch sensitivity to WT



Conclusions

- Unlike adult mice, P7-11 day old mice with the Piezo2 GOF mutation did not exhibit significantly lower firing frequency during stretch when compared to WT mice.
- This suggests that sensitivity to stretch in mice with a Piezo2 GOF mutation changes as the mice age.
- Future studies should examine the expression levels of Piezo2 and other cation channels responsible for MSA excitability in mice of various ages to determine what is changing over time with the GOF mutation.
- Understanding these time dependent changes in MSA excitability with the Piezo 2 GOF mutation could help identify treatment options for DAG5.