KIF1A Mouse Models

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Visit kif1a.org/2019Conference to watch a recording of this presentation.

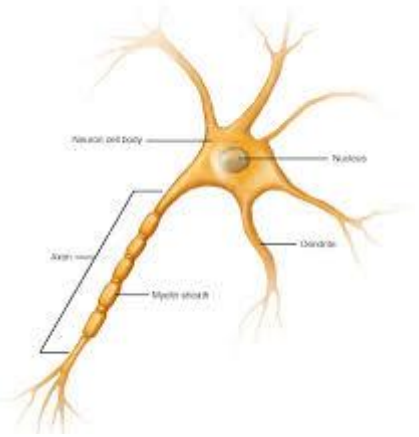
THE WALL STREET JOURNAL.

"We need a mouse" campaign

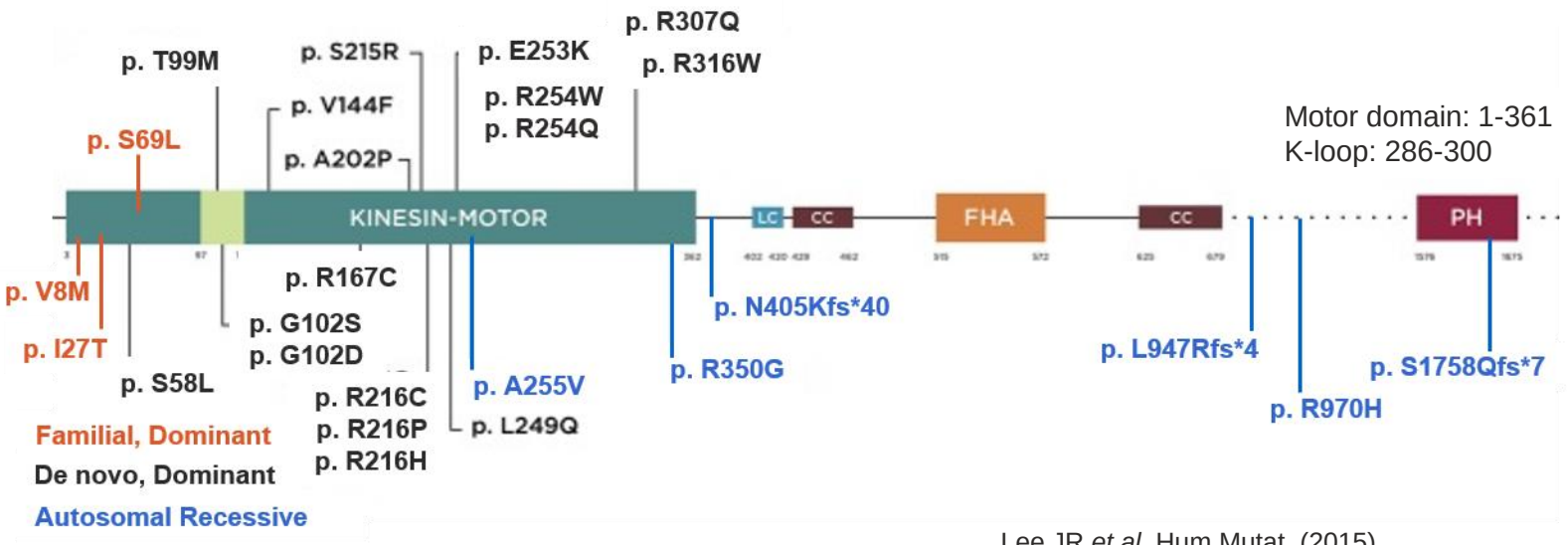
U.S.

On the Way to a Rare-Disease Cure, Parents Tackle the High Price Tag of Research

Structure function of the protein

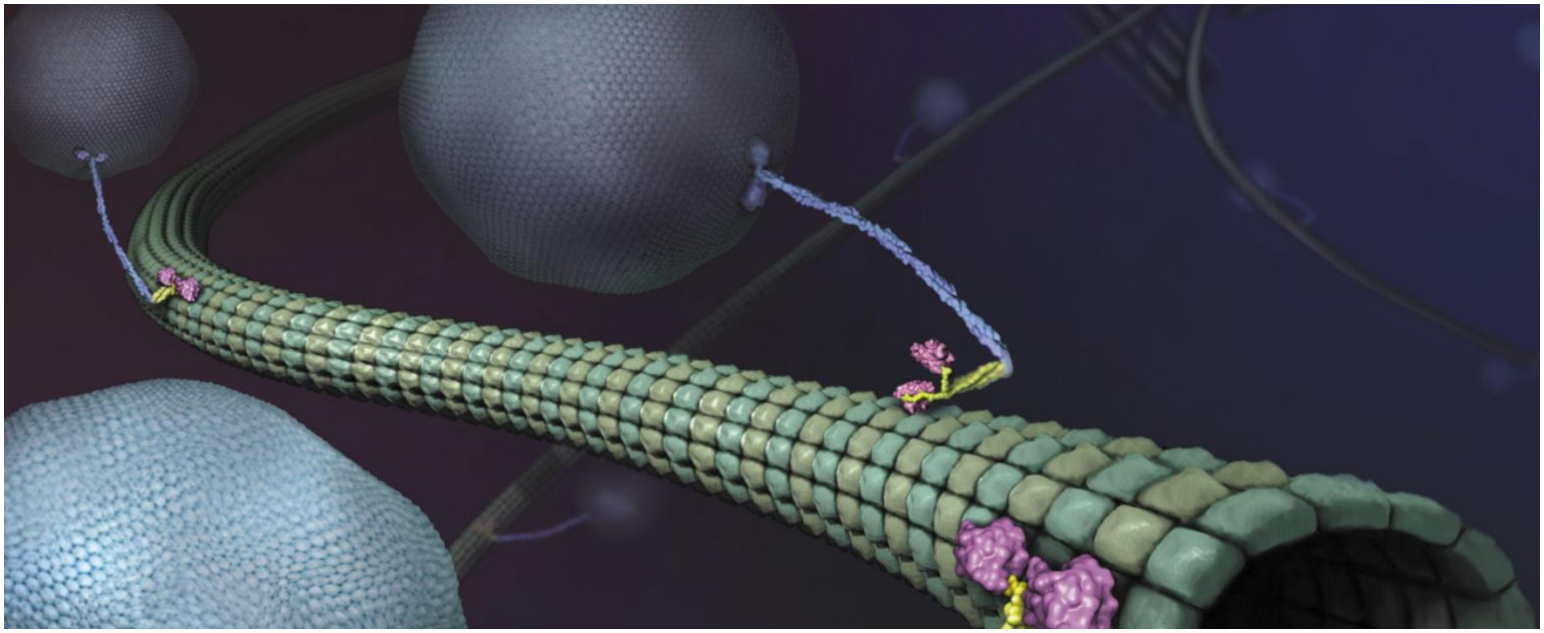


- Most of *KIF1A* mutations are identified in the motor domain resulting in a more severe phenotype.
- Current clinical variants identified in *KIF1A* can be classified into three category – autosomal recessive, *de novo* dominant, and familial dominant.



Lee JR *et al.* Hum Mutat. (2015)
Esmaeeli Nieh S *et al.* Ann Clin Transl Neurol. (2015)
https://www.kif1a.org

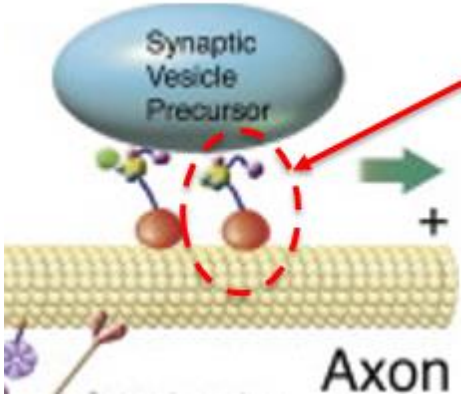
Anterograde Axonal Transport



KIF1A is a kinesin-family motor involved in the axonal transport of synaptic vesicle precursors along microtubules.

Anterograde axonal transport supplies organelles and protein complexes throughout axonal processes to support neuronal morphology and function.

What are the mouse tools you need in your toolbox to match therapeutic strategies?



Need to understand the basic biology:

What does a complete loss of function do in mouse?

What do patient specific mutations look like in a mouse?
Can you fix the wheel on a train?

What if you can knock down the disease causing allele?
how much do you have to knock it down? 10 or 90%?

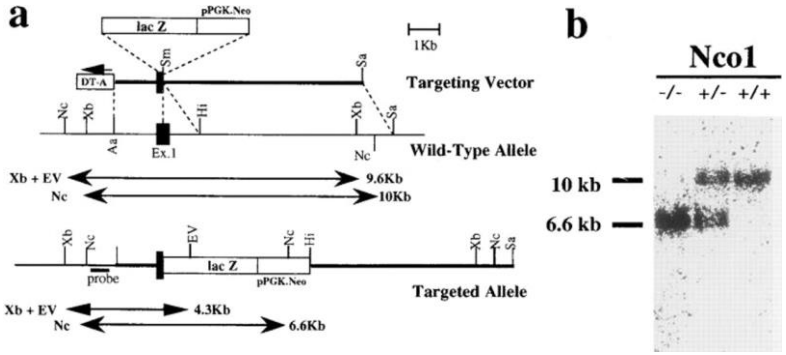
Can adding more Kif1a outcompete the dominant negative gene?
Flood the track with good trains

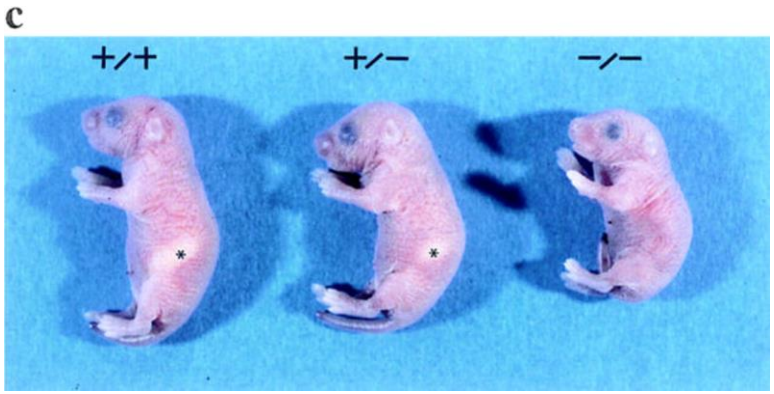
Is too much Kif1a a bad thing?
Need to know--

Existing KIF1A mouse models

KNOCK-OUT MOUSE

- **Kif1a^{tm1Noh}**





- ❑ Null mice were born alive but died within 24h because they did not suckle milk.
- ❑ Show sever motor and sensory abnormalities
- ❑ Reduced synaptic vesicles at synaptic terminals were observed.
- ❑ Focal neuronal death were detected in brain.

- ❑ In short, mice to not tolerate loss of Kif1a

Yonekawa Y *et al.* 1998, J. Cell Biol

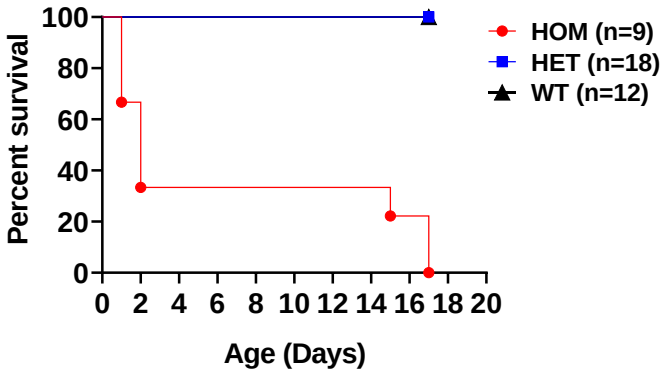
New efforts for KIF1A
preclinical models

- **C57BL/6J-Kif1a<em2(I304I,P305L)Lutzy>**

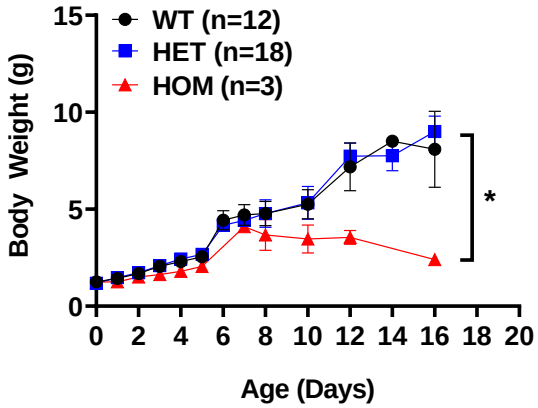
  Knock-in strains. CRISPR/Cas9 mediated point mutations, I304I and P305L, are introduced to *Kif1a* gene

  - Body weight, neurological scores, strength, electrophysiology, etc

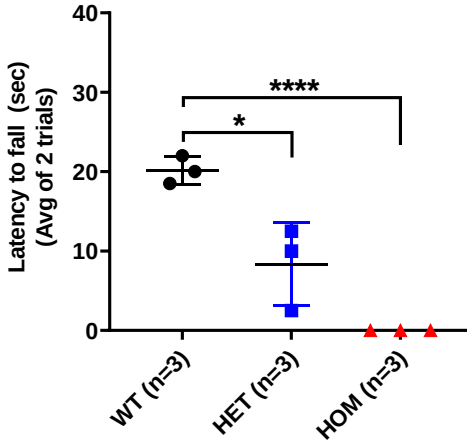
Survival



Body Weight



Hind limb suspension test:

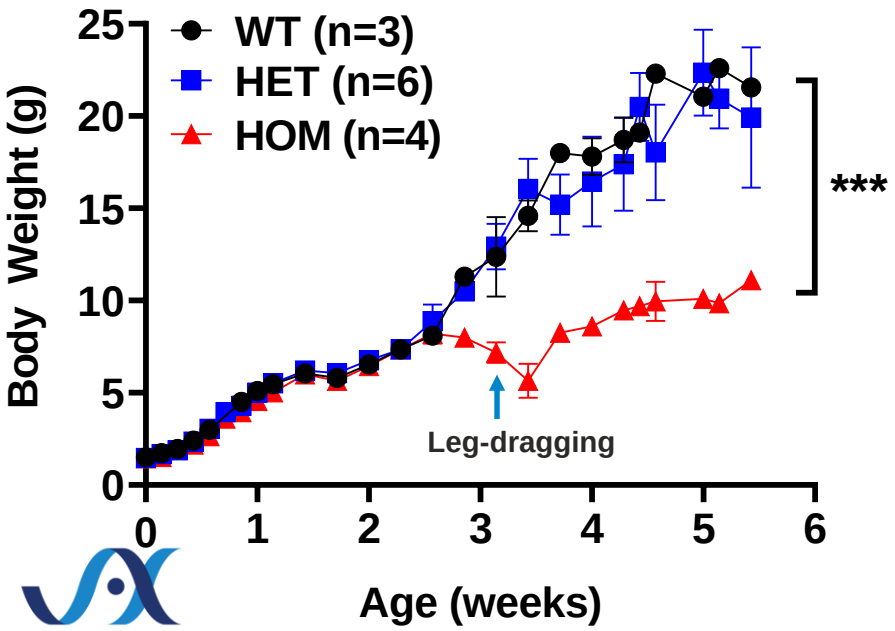


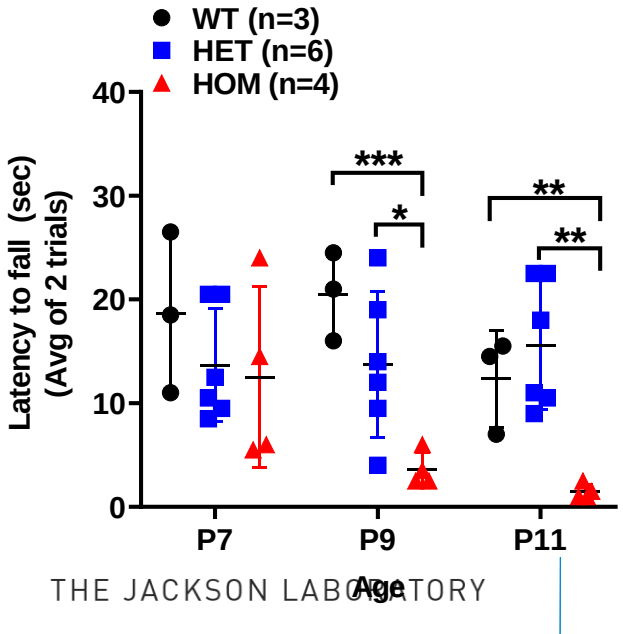
This mutation is not well tolerated when all the trains on the track are stuck. But when half the trains are defective, we see subtle changes

Existing KIF1A mouse models

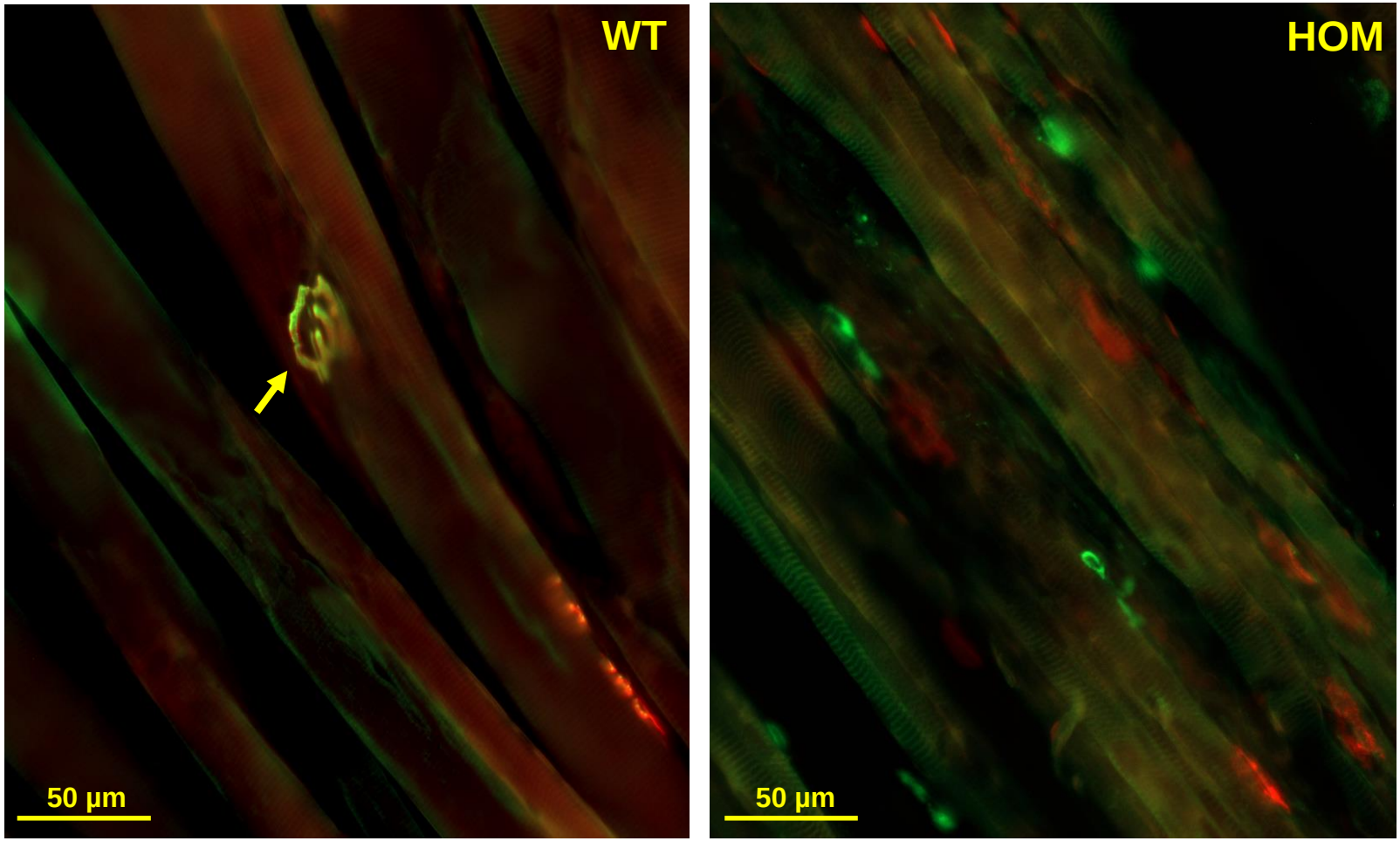
leg dragger (spontaneous from JAX)

- JR#16894 strain has a spontaneous L181F missense mutation in Kif1a gene.
- Before 2 weeks old of age, HOM has similar body weight compared to their WT and HET littermates. At 3 weeks of age, HOM is smaller and lighter compared to their littermates with leg-dragging phenotype.
- Significant hind limb weakness is observed in HOM neonates as early as 9 days old of age.





Neuromuscular junction (NMJ) staining in Kif1a leg-dragger model



Green: Presynaptic Vesicle
Red: postsynaptic neuromuscular junction

Additional efforts for KIF1A

preclinical models to answer therapeutic questions

- **C57BL/6J-TG(CAG-Kif1a)**
  - **A mouse model to that expresses KIF1A in a constitutive manner**
  - **Allows us to genetically cross this mouse to other Kif1a models to answer the questions:**
    1. **Can overexpression rescue the Kif1a mouse?**
    2. **Is over expression tolerated?**

- **C57BL/6J-TG(LSL-CAG-Kif1a)**
  - **This mouse model allows us "turn on" the Kif1a gene at any time in the life or disease course of the mouse**
  - **Allows us to genetically cross this mouse to other Kif1a models to answer the questions:**
    3. **Can we turn on the Kif1a gene later in life, and have a benefit?**

Children with rare genetic disease find comfort in this first-ever meeting

Henry Quindara, USA TODAY Published 8:34 a.m. ET Aug. 28, 2019

Dear Yi-Ju and Cat,
From the bottom of our hearts, thank you. Thank you for your work, your presentation, for all you do. Thank you for being there with us, and thank you for loving Sus and so many kids like her. You guys mean the world to us. Here's s picture from lunch!
Thanks so much!

Lutz Lab

Laurent Bogdanik
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Jonathan Newell
Elizabeth Rocker
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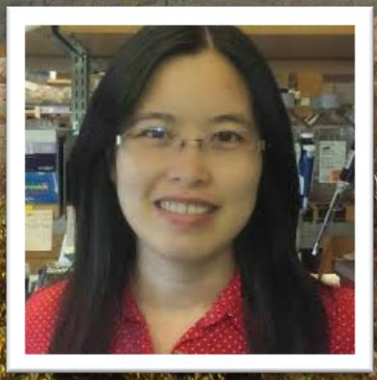
Hanna Knowleton
Zach Beaudry
Amada Dolton
Mike Day
Somedatta Ray
Saurabh Tata
Jenn Cook

Collaborators and colleagues
Wendy Chung
Luke Rosen
All the KIFA1 families

Aamir Zuberi



Ji-Yu Chen