



Research Roundtable Community Summary – August 26, 2020

KIF1A.ORG's second Research Roundtable meeting was focused on one theme: "Help KIF1A.ORG Help You." This meeting was held as an open forum discussion, with a series of questions posed by KIF1A.ORG to spark conversation and collect valuable input from researchers. With our research network actively growing, it's important for KIF1A.ORG to understand the needs and research goals of network members. Our aim is to help align KIF1A research strategy across institutions around the world to 1) avoid duplicative research and 2) expedite discovery. This is how we get to treatment faster!

Attendance



19 RESEARCHERS



13 INSTITUTIONS



3 KIF1A.ORG REPS



2 CZI REPS



3 CONTINENTS

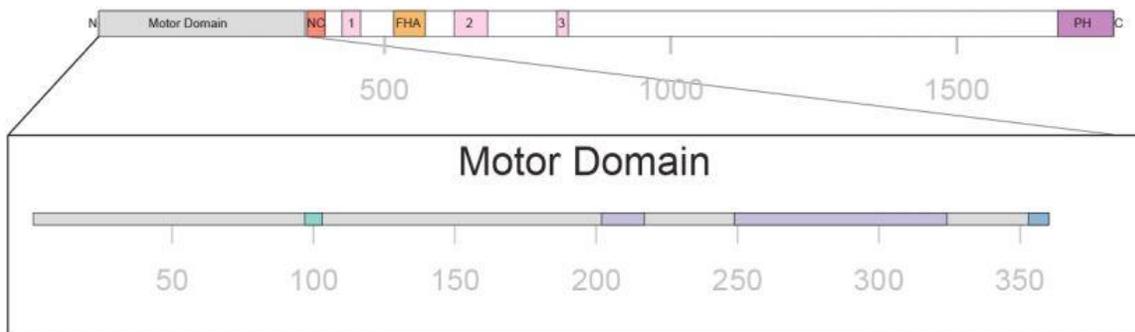


10 SUBSPECIALTIES

What We Learned

- Identified gaps in our understanding of KIF1A
 - What are the cargos of KIF1A?
 - We have good data on *some* cargos of KIF1A, but there are likely more. Identifying KIF1A cargo will inform us further about KIF1A's role in our nervous system.
 - How do different KIF1A variants present at a clinical level?
 - As most of our research network falls under the "basic science" category (i.e., researchers studying KIF1A under a microscope in the lab), many are not as familiar with the clinical aspects of KAND. Luckily, the recent [pre-print](#) out of Chung Lab is a great tool to provide researchers who want to learn more about how patients are effected by KAND. These insights would not be possible without families like you participating in the [Natural History Study!](#)

- Research Network members are interested in longitudinal data. This would be data that follows KAND progression *over time*.
 - What are the cellular implications of KIF1A mutation?
 - Most KIF1A variant characterization has been conducted at the molecular and the clinical level.
 - While there is some research at the cellular level, it is comparatively understudied.
 - Characterizing variants at the cellular level is needed to help us understand how KIF1A mutation impacts the structures and components in our nervous system.
 - What's going on outside of the KIF1A motor domain?
 - The KIF1A motor domain is like the engine that allows KIF1A to run and transport cargo. The motor domain is well studied across all kinesin proteins. Furthermore, the majority of pathogenic KIF1A variants are located in the motor domain, helping shape our understanding KAND.
 - However, KIF1A is *much* more than just a motor domain. We commonly refer to the region of KIF1A outside of the motor domain as the “stalk” region. We know very little about the KIF1A “stalk” particularly on the structural level. Learning more about the KIF1A “stalk” will be very helpful information to have to further understand how KIF1A behaves, which has implications for therapeutic development.



Functional domains

- Neck coil ■ Coiled coil ■ Forkhead associated ■ Pleckstrin homology

Microtubule binding regions

- P-loop ■ Switch I ■ Switch II ■ Neck linker

Domains and regions of the KIF1A gene. Source: Chung Lab.

- Model systems
 - Our research network agreed that we can and should use KIF1A model organism systems more.

- During this meeting, we had researchers who use a variety of different model organisms to study KIF1A/KAND:
 - Mouse
 - *Drosophila* (fruit fly)
 - *C. elegans* (worm)
 - Zebrafish
 - Each model system has its strengths and weaknesses. One of the unanimous strengths of all model systems is *time*, meaning it is much faster to conduct longitudinal studies in model organisms than it is in humans.
 - We think it would be a great idea to have a “model organism” sub-group of the Research Roundtable.
- KIF1A’s relationship with other KIF proteins
 - Sometimes we see the *same* KIF1A mutation in other kinesin proteins.
 - Most recently, researchers are finding an overlap in mutations between KIF1A and KIF5A.
 - KIF5A mutations have been correlated to both HSP and ALS.
 - KIF1A and KIF5A do have some overlap in the cargo that they transport in our nervous system so it is not entirely surprising that they can present with similar clinical phenotypes.
 - What does this mean?
 - When studying KIF1A mutations, it is important to cast a broad net. Sometimes the information we can gather from a totally different protein can help us learn more about KIF1A!
- We posted a few polling questions for attendees during the meeting, and found:
 - Most KIF1A researchers are already collaborating with each other.
 - This is great! Now we want to encourage these collaborations across scientific subspecialties.
 - Most of our Research Network found KIF1A.ORG by either an internet search or through a colleague.
 - The best form of support that KIF1A.ORG can give our Research Network is through connections to other researchers.
 - 2nd place: funding
 - 3rd place: research materials (i.e., cell lines, mouse models)

What’s Next?

- September Research Roundtable scheduled September 24.
 - Topic: Therapeutic Strategies for KAND.

When asked “what excites you most about KIF1A/KAND therapeutic development,” Dr. Richard McKenney from University of California, Davis replied:

There are so many other motor proteins I could study. But this community of KIF1A families excites me.