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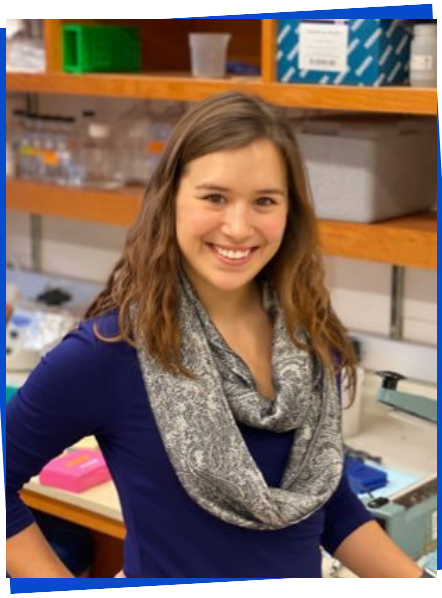

Presentation: A brief history of KIF1A: From gene discovery to disease mechanism(s) [read here]

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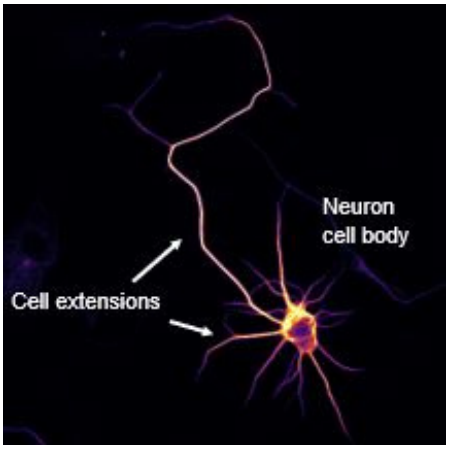
A History of Kinesin Discovery

Our understanding of KIF1A begins with the discovery of kinesin motors in 1985. This ground-breaking finding opened the doors to scientific progress into how cellular components move around within a cell. A cell contains numerous structures and organelles which sometimes need to move to specific locations to perform their required functions. One way that these components are transported is by kinesin motor proteins, which can act like 'trains' to carry the cargos along cellular 'tracks' known as microtubules. Fittingly, the name 'kinesin' is derived from the Greek verb kinein meaning 'to move'. KIF1A, which was discovered in the early 1990's, is a special type of kinesin motor that is present in neurons, the major cell type in the brain. Unlike many cell types which remain roughly spherical, neurons exhibit unique architectures and form cellular extensions that can reach up to 1 meter in length. Neurons therefore rely heavily on motor proteins to carry cargos across these vast distances and maintain cellular health.



Microtubules (yellow) extend into long extensions emanating from the neuron cell body. Source: Jayne Aiken and Georgia Buscaglia, University of Colorado Anschutz.

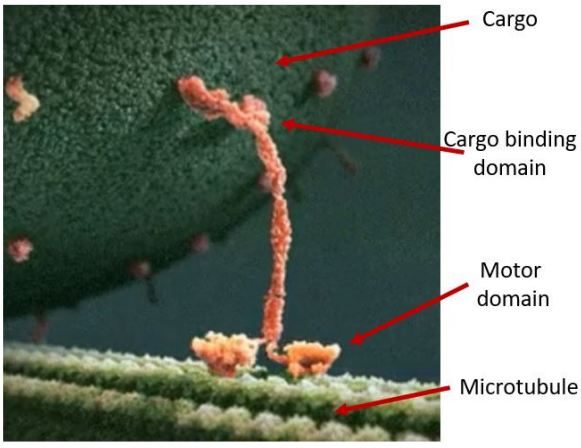


Image of a kinesin carrying cargo while "walking" along a microtubule from John Lieber's "Life of the Cell" (2006) with labels provided by Lia Boyle.

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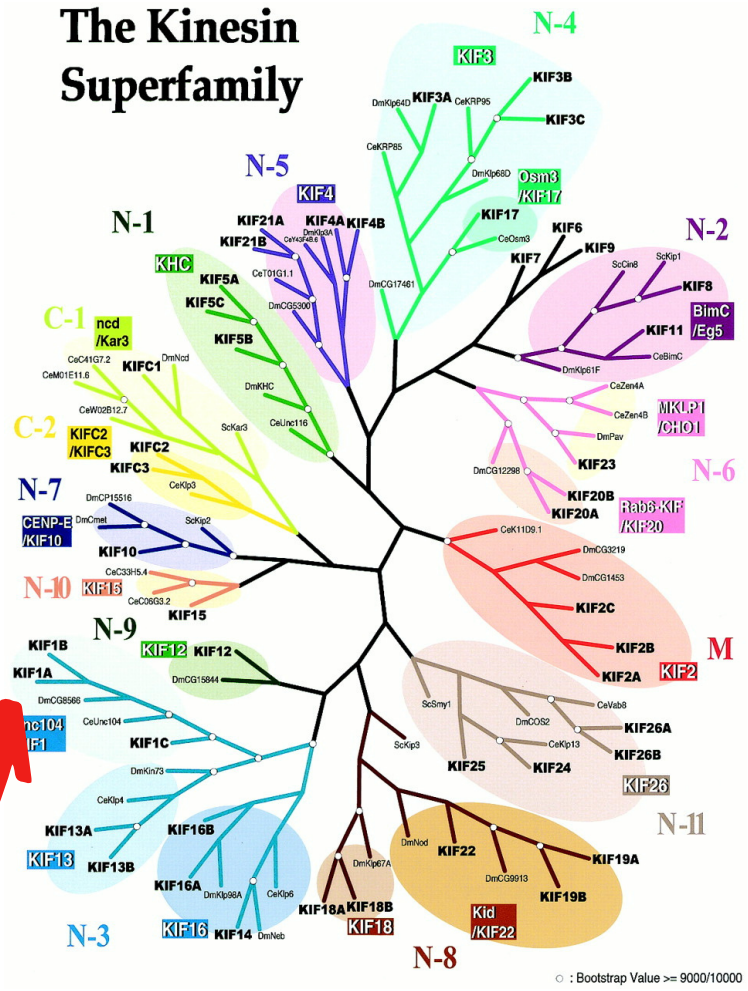
What Makes KIF1A Unique?

In human cells, distinct types of kinesins can be expressed depending on the cell's needs. The different kinesins are grouped into families based on common characteristics. KIF1A belongs to the kinesin-3 family (labeled N3 in figure below). Kinesin motors in this family have been shown by scientists to be 'marathon runners', capable of moving on microtubules for longer distances than other kinesins. KIF1A's ability to run long distances is important for the distribution of neuronal cargos into cellular extensions.

Another unique characteristic of kinesin-3 motors is the way they exist in the cell before actively transporting cargos on microtubules. To transport cargos around a cell, kinesin motors use their motor domain 'feet' to step along a microtubule. One kinesin motor protein (known as a monomer) contains only one 'foot'. Therefore, two kinesin proteins must link together (forming a dimer) to effectively 'walk' along the microtubule using two 'feet'. Unlike kinesin motors belonging to other families, which always exist as dimers containing two 'feet', kinesin-3 motors exist as monomers in a one 'foot' inactive state, floating around the cell until they bind cargo and dimerize. This dimerization step allows two KIF1A motors to link together, providing the necessary two 'feet' needed to activate stepping movement along the microtubule. This monomer-to-dimer activation finding was controversial in the motor field and took many years of research for scientists to reach a consensus. Each step in understanding how KIF1A acts in a cell gives us a better grasp on its important roles and how they may be altered in disease.

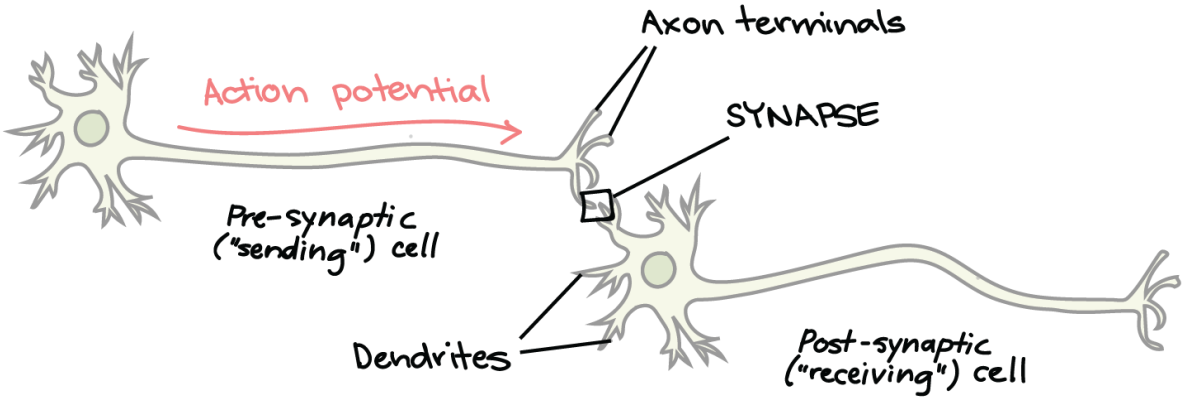
KIF1A belongs to the Kinesin-3 family, labeled N-3 in blue.



Click the image for a larger copy of The Kinesin Superfamily "tree." Source: Miki et al. "All kinesin superfamily protein, KIF, genes in mouse and human" 2001.

KIF1A Traffics Many Types of Cargo

Inside neurons, KIF1A walks along microtubules in the long cellular extensions, called axons and dendrites, to distribute important cellular components. But what are KIF1A's cargos and how does the cell know where to distribute them? These questions are still under active investigation, but we do have some insights due to recently published research. Numerous cargos (listed in accompanying presentation, slide 36) have been confirmed to be trafficked by KIF1A. Some of them are carried into the axon, which houses presynapses, while others are trafficked into dendrites, which host postsynapses. The ability of KIF1A to enter both axons and dendrites is another unique characteristic, as a different neuronal kinesin motor family, kinesin-1, is restricted to the axon. KIF1A cargos include important synaptic components; when KIF1A motor activity is disrupted in neurons, synaptic impairment occurs. Therefore, KIF1A trafficking is important for both axonal and dendritic health.



A drawing of two neurons. Source: Khan Academy.

Cellular Mechanisms of KIF1A Regulation

Microtubules in neurons are tightly regulated to provide tracks for motors and structural integrity for the neuron's long extensions. The regulation of microtubules impacts the way KIF1A and other kinesins walk along them. Microtubules can be decorated with modifications and proteins that vary by cellular location. Specifically, KIF1A is impacted by microtubule polyglutamylation (addition of the amino acid glutamate to the outside of microtubules). Additionally, its movement is restricted by the presence of the proteins Tau, MAP7, and MAP2C on microtubules and allowed on microtubules covered in DCX, DCLK1, and MAP9. KIF1A motors also behave differently depending on where along the microtubule they are walking. Because of their 'marathon runner' tendencies, KIF1A motors often walk to the end of microtubules, where they rapidly unbind due to structural differences found at microtubule ends. Numerous microtubules end at presynapse regions in the axon; therefore, the ability of KIF1A to detach at microtubule ends helps deliver synapse-specific cargos to the correct place in the cell.

Another unique aspect of KIF1A regulation is how long the motor exists in the cell. Inside cells, new proteins are made (synthesized) and old proteins are destroyed (degraded) at regular intervals. Some proteins stick around for long periods, while others are degraded and renewed rapidly. New research suggests that KIF1A motors are synthesized and degraded much more rapidly than other kinesins. The importance of this finding is still unclear.

Implications of KIF1A Mutation

Lastly, mutations in the KIF1A gene have been identified in patients diagnosed with KIF1A Associated Neurological Disorder (KAND). An important prong of KIF1A research relates to the nature of KIF1A mutants and how they alter important cellular functions to lead to disease. See the last page of this document for a diagram of known mutations of the KIF1A gene. While the nature of KAND mutations remains a point of discussion in the field, recent studies propose that KIF1A mutations can act in two distinct ways: 1) KIF1A mutants can act as gain-of-function mutants, where the mutant motor acts to 'gum up the works' and alter important KIF1A roles, or 2) KIF1A mutants can act as loss-of-function mutants, where the mutant motor is incapable of performing its function and the cell doesn't have enough KIF1A motors to meet its needs. Some gain-of-function mutants cause the motor to be too active in the cell (hyperactive). This causes cargos to be misplaced further along the cellular extensions than they should be. Loss-of-function mutants are more likely to stop the KIF1A motors from dimerizing, binding cargo, or walking along microtubules, all of which would keep the KIF1A mutant from trafficking its cargo. Additional studies must be performed to determine which of the numerous KAND mutations act as gain-of-function or loss-of-function. This knowledge will be essential in understanding how KAND mutants alter cellular function to ultimately manifest as clinical symptoms.

Summary

KIF1A is an important kinesin motor protein that is responsible for trafficking many different cargos along microtubules throughout the sprawling neuron. It belongs to a kinesin family described as 'marathon runners', meaning that the motors can walk long distances before falling off the microtubule track. Regulation of the microtubule influences how KIF1A walks and where it delivers cellular components. KIF1A mutations can lead to KIF1A Associated Neurological Disorder and likely span both gain-of-function and loss-of-function mechanisms to disrupt the positioning of cargos through the neuron. Continuing scientific research will provide insight into additional KIF1A roles and regulation in the cell, how disease mutants alter KIF1A's normal cellular jobs, why these changes lead to disease symptoms, and how to treat them.

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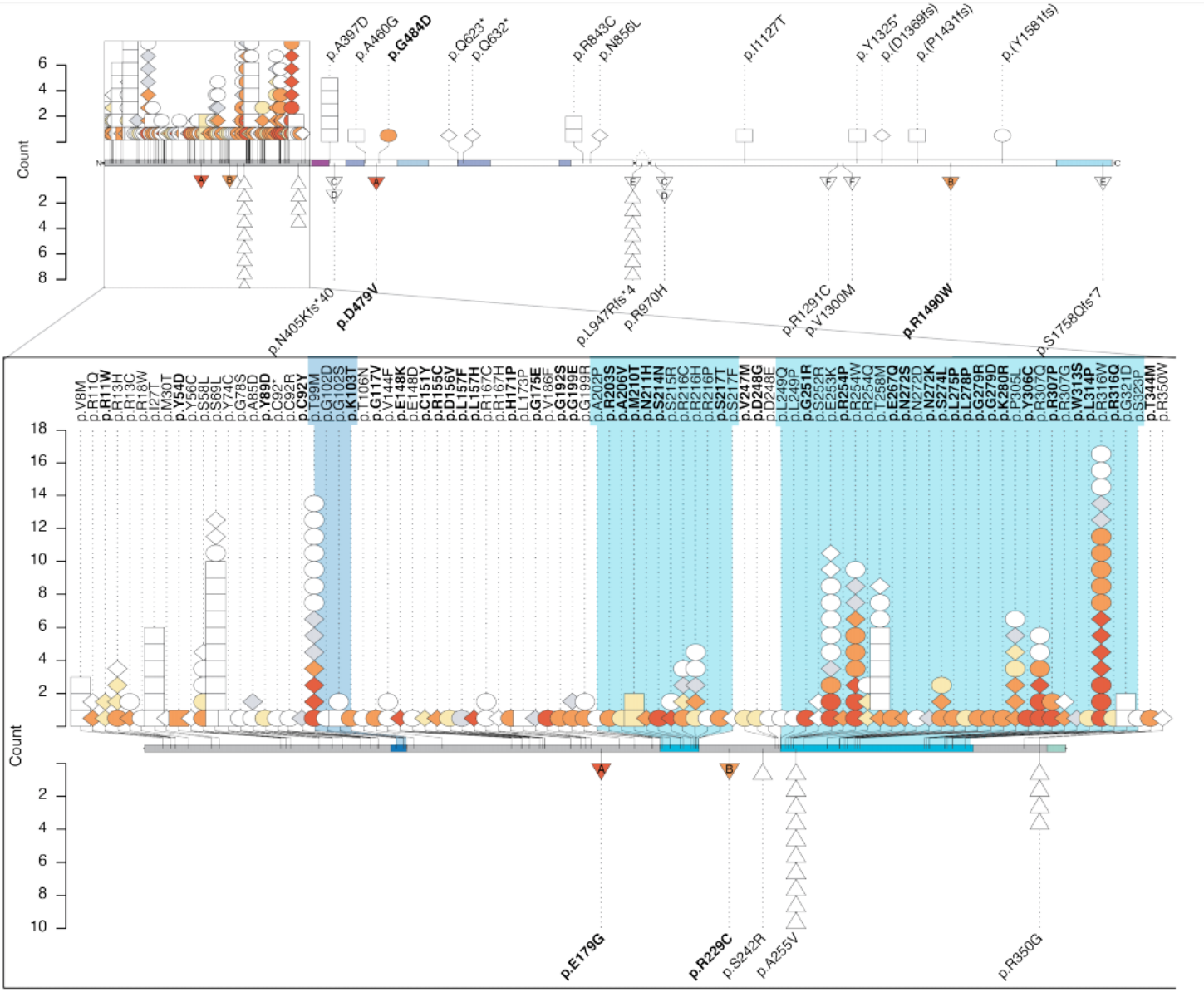

A diagram of known mutations of the KIF1A gene (as of August 2020). Source: Boyle et al. "Genotype and defects in microtubule-based motility correlate with clinical severity in KIF1A Associated Neurological Disorder" 2020.

Questions or comments about this Research Simplified? Send an email to dvlessard@kif1a.org.