

SPOTLIGHT

Different variants, different cellular outcomes: Balanced KIF1A activity shapes synapse development

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In this issue, Aiken et al. (<https://doi.org/10.1083/jcb.202601034>) show that pathogenic KIF1A variants induce distinct effects on axonal transport, cargo distribution, and neuronal development. Their findings suggest that balanced KIF1A activity is required for proper synaptic development and function.

Axonal transport is essential for synapse formation and the maintenance of neuronal function. KIF1A is a kinesin superfamily motor protein and transports synaptic vesicle precursors (SVPs) and active zone precursors. Given the importance of KIF1A in the axonal transport of synaptic cargos, it is not surprising that pathogenic variants of KIF1A cause neurological diseases (1). What is really surprising is the number of pathogenic variants identified in the KIF1A gene. About 200 disease-associated variants have been reported so far, and new variants continue to be identified (2). The clinical features are very diverse, ranging from motor neuron abnormalities such as spastic paraplegia to sensory neuron defects, including visual defects and reduced pain sensation, and cognitive defects such as intellectual disability. The severity of these symptoms is also diverse among patients. This broad spectrum of neurological symptoms caused by pathogenic KIF1A variants is collectively referred to as KIF1A-associated neurological disorder (1).

Disease-associated KIF1A variants provide useful clues for studying the cell biology of KIF1A and axonal transport. Single-molecule assays and analyses using model organisms have revealed that pathogenic KIF1A variants can affect KIF1A activity in diverse ways, ranging from loss-of-function and dominant-negative effects

to hyperactivation (1, 3, 4, 5). For example, the hypomorphic KIF1A(P305L) mutation impairs microtubule association by altering the conformation of the K-loop region, which is important for microtubule binding (6). The *Drosophila* counterpart of the hyperactive KIF1A(R350G) variant, DmUNC104(R348G), promotes dimerization of the full-length motor, suggesting that enhanced dimerization contributes to KIF1A hyperactivation (7). Aiken et al. (8) now take advantage of this functional diversity to ask how different changes in KIF1A motor activity are translated into neuronal phenotypes. They compared three pathogenic variants: a null mutation (C92*) (9), a hypomorphic mutation (P305L) (5, 6), and a hyperactive mutation (R350G) (4) (Fig. 1). These three variants induced different effects on neuronal morphology. The first difference was observed during early neuronal development. Neurite outgrowth was strongly affected in KIF1A(C92*) neurons and was also impaired, although less severely, in KIF1A(P305L) neurons. In contrast, neurite development in KIF1A(R350G) neurons was comparable with that in control neurons. Therefore, reduced KIF1A activity, but not hyperactivation of KIF1A, interferes with early neurite development. In addition, Aiken et al. report that the three variants had divergent effects on axonal transport, which causes distinct cargo

distribution. P305L reduced the velocity and flux of SVPs, whereas KIF1A(R350G) increased both of these parameters. These differences are consistent with the motor activity in vitro (4, 5). Surprisingly, complete loss of KIF1A in KIF1A(C92*) neurons had relatively little effect on bulk SVP motility, suggesting that other motors, such as KIF1B β , may compensate for the loss of KIF1A. Despite these differences in motility, both KIF1A(C92*) and KIF1A(P305L) caused retention of presynaptic cargo in the soma and depletion of cargo from presynaptic sites in the axon. In contrast, the hyperactive R350G mutation reduced somatic localization of SVPs and increased localization in the axon. More transport, however, did not mean better delivery. Although KIF1A(R350G) increased SVP transport, SVPs failed to accumulate at discrete sites along the axon, and the density of stable SVP-positive vesicle pools was reduced by about 50% (Fig. 1). Local microtubule dynamics are thought to help pattern presynaptic cargo delivery sites along the axon (10, 11). In KIF1A(R350G) neurons, this relationship was weakened, suggesting that hyperactive KIF1A may fail to respond appropriately to these local cytoskeletal cues. Thus, efficient transport and accurate spatial delivery are not equivalent. These distinct cellular defects were reflected in neuronal function. KIF1A(C92*) and KIF1A(P305L)

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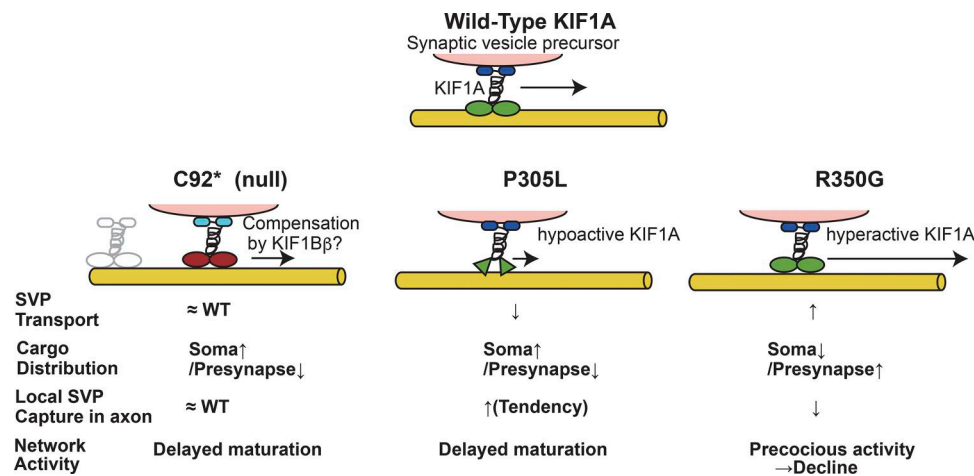


Figure 1. Balanced KIF1A activity is required for coordinated synaptic cargo transport and neuronal development. Pathogenic KIF1A variants produce distinct effects on SVP transport, cargo distribution, local SVP capture, and network activity. C92* and P305L variants reduce cargo delivery to presynaptic sites and delay neuronal maturation, although bulk SVP motility is largely preserved in C92* neurons, potentially through compensation by KIF1Bβ. In contrast, R350G enhances SVP transport and presynaptic cargo accumulation but reduces stable SVP capture along axons and causes precocious network activity followed by a decline in activity. Arrows indicate changes relative to WT; ≈WT indicates little detectable change.

neurons showed delayed synaptic maturation, whereas KIF1A(R350G) neurons displayed an earlier onset of neuronal network activity compared with control neurons. However, this earlier network activity was followed by a sharp decline in activity at later stages. Thus, both reduced and excessive KIF1A activity disrupt synaptic development, but they do so in different ways: loss-of-function variants delay maturation, whereas hyperactive KIF1A accelerates the onset of network activity but impairs its maintenance.

These findings raise broader questions in cell biology. These data implicate that neuronal development depends not simply on the amount of cargo transported, but on the appropriate level, timing, and spatial control of KIF1A-dependent transport. The requirement for balanced KIF1A activity is also relevant to the safety of allele-specific ASO therapy. Ziegler et al. treated a patient carrying the P305L variant with an allele-specific ASO designed to specifically suppress the expression of the mutant allele (12). Because the present study examined homozygous mutant neurons, analysis of heterozygous models that more closely reflect the patient genotype will be important.

Such models should help determine how WT and mutant KIF1A function together and how selective silencing of the P305L allele affects neurons that retain one WT KIF1A allele. A broader challenge in cell biology is to understand how neurons establish this balance in the first place. One possibility is that neurons monitor cargo distribution, synaptic activity, or other aspects of their developmental state and feed this information back to regulate KIF1A-dependent transport. Whether such feedback exists, what is detected, and how this information is transmitted to the motor machinery remain open questions. Answering them should reveal how axonal transport is coordinated with cargo distribution, synapse formation, and the maturation of neuronal networks.

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