KIF1A

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Neuronal function depends on axonal transport by kinesin superfamily proteins (KIFs). KIF1A is the molecular motor that transports synaptic vesicle precursors, synaptic vesicles, dense core vesicles and active zone precursors. KIF1A is regulated by an autoinhibitory mechanism; many studies, as well as the crystal structure of KIF1A paralogs, support a model whereby autoinhibited KIF1A is monomeric in solution, whereas activated KIF1A is dimeric on microtubules. KIF1A-associated neurological disorder (KAND) is a broad-spectrum neuropathy that is caused by mutations in KIF1A. More than 100 point mutations have been identified in KAND. In vitro assays show that most mutations are loss-of-function mutations that disrupt the motor activity of KIF1A, whereas some mutations disrupt its autoinhibition and abnormally hyperactivate KIF1A. Studies on disease model worms suggests that both loss-of-function and gain-of-function mutations cause KAND by affecting the axonal transport and localization of synaptic vesicles. In this Review, we discuss how the analysis of these mutations by molecular genetics, single-molecule assays and force measurements have helped to reveal the physiological significance of KIF1A function and regulation, and what physical parameters of KIF1A are fundamental to axonal transport.