The Kinesin Superfamily Handbook

Transporter, Creator, Destroyer

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Claire T. Friel

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4 The Kinesin-3 Family
Long-Distance Transporters

Nida Siddiqui and Anne Straube

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CONTENTS

The Kinesin-3s are a family of cargo transporters. They typically display highly processive plus-end-directed motion, either as dimers or in teams, formed via interaction with cargo.

4.1 EXAMPLE FAMILY MEMBERS

Mammalian: KIF1A, KIF1B, KIF1C, KIF13A, KIF13B, KIF14, KIF16B
Drosophila melanogaster: UNC-104
Caenorhabditis elegans: UNC-104, KLP6

4.2 STRUCTURAL INFORMATION

The Kinesin-3 family is classified into five subfamilies, named Kinesin-3A/KIF28, -3B/KIF16, -3C/KIF1, -3D/KIF13 and -3E/KIF14 (Miki et al., 2005, Wickstead and Gull, 2006). Members of the family possess an N-terminal motor domain, followed by a neck domain, a subfamily-specific forkhead-associated (FHA) domain (Westerholm-Parvinen et al., 2000), typically several regions of predicted coiled-coil and a diverse C-terminal tail containing short coiled coils, with lipid- and protein-interaction regions that aid in cargo- as well as adapter-binding (Figure 4.1A).

The Kinesin-3 motor domain contains a characteristic stretch of lysine residues in Loop 12, known as the K-loop. This loop forms part of the microtubule-binding surface and interacts with the glutamate-rich C-terminal tail of β-tubulin. This

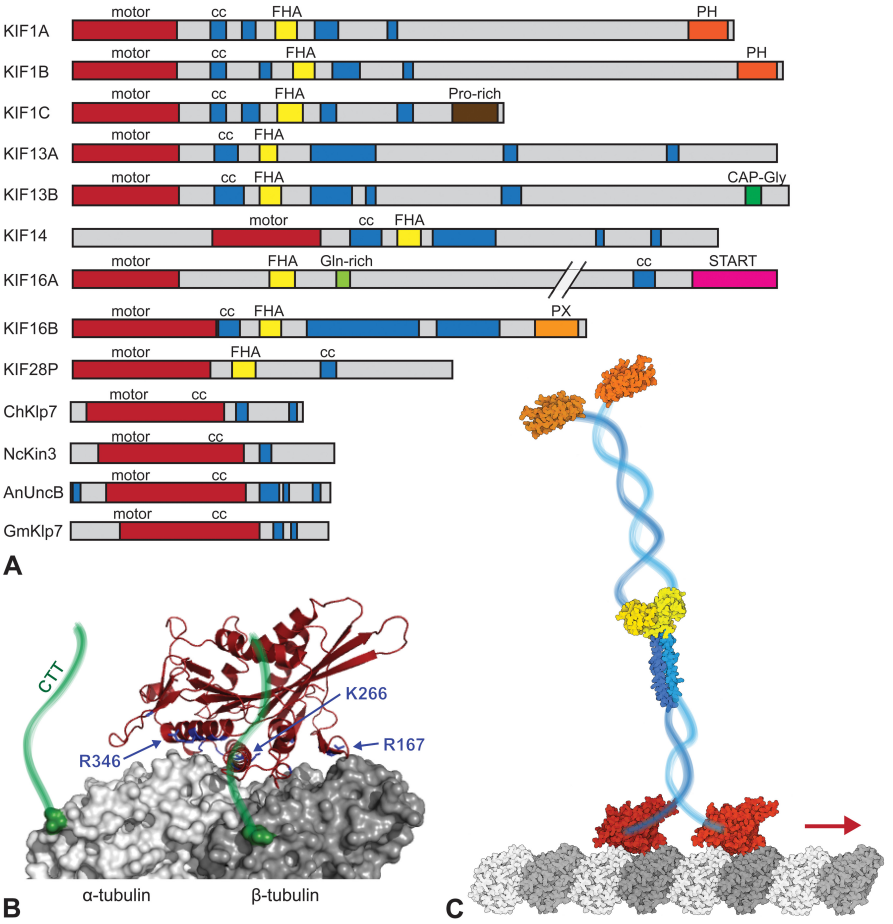

FIGURE 4.1 Structure of members of the Kinesin-3 family. (A) Domain organisation in Kinesin-3s shows the characteristic N-terminal location of the motor domain, FHA domain and tail, with several short coiled-coil (CC) regions in addition to a variety of protein- or lipid-interaction motifs. (B) KIF1A motor domain (dark red) bound to tubulin (grey) with C-terminal tubulin tails indicated in green. Key residues specific for the Kinesin-3 family that increase processivity of KIF1A (Atherton et al., 2014, Scarabelli et al., 2015) are highlighted in blue. PDB: 4UXP. (C) Composite of a dimeric Kinesin-3 with motor domains (red) from KIF1A, FHA domain (yellow) and CC1 (blue) from KIF13B and PX domain (orange) from KIF16B. PDB: 4UXP, 5DJO and 2V14, using Illustrate (Goodsell et al., 2019).

interaction has been reported to influence the microtubule on-rate for the 3B, 3C and 3D subfamilies (Soppina and Verhey, 2014, Rogers et al., 2001, Lessard et al., 2019, Matsushita et al., 2009). The K-loop has also been proposed to enable diffusive movement on the microtubules for a subset of Kinesin-3s (Okada and Hirokawa, 1999, 2000), as well as facilitating Kinesin-3 motors to work in teams (Rogers et al., 2001, Soppina and Verhey, 2014). Comparison of high-resolution cryo electron microscopy structures of Kinesin-1 (KIF5A) and Kinesin-3 (KIF1A) motor domains bound

to microtubules in different nucleotide states, combined with molecular dynamics simulations, suggests that multiple amino acid differences spread over the microtubule-binding interface contribute to the 200-fold greater affinity of Kinesin-3 for microtubules compared with Kinesin-1 (Scarabelli et al., 2015, Atherton et al., 2014). This greater affinity results in increased processivity of dimeric Kinesin-3 motors (Atherton et al., 2014). The key processivity-determining residues are Arg167 in loop 8, Lys266 in loop 11 and Arg346 in α-helix 6 of KIF1A (Scarabelli et al., 2015) (Figure 4.1B).

Most Kinesin-3s act as dimers, with coiled-coil regions enabling motor dimerisation as well as interaction with binding partners (Peckham, 2011) (Figure 4.1C). The neck coil has been reported to drive dimerisation for KIF1A, KIF13A and KIF13B (Hammond et al., 2009, Soppina et al., 2014), whereas for KIF1C, the fourth coiled-coil domain is sufficient to promote dimerisation (Dorner et al., 1999). For the *C. elegans* Kinesin-3, Unc-104, coiled-coil regions mediate interaction with dynein/dynactin subunits (Chen et al., 2019). Recent X-ray crystallographic structures of monomeric and dimeric conformations of KIF13B confirm that coiled-coil 1 is crucial for maintaining autoinhibition of the motor domain (Ren et al., 2018).

FHA domains are phospho-peptide recognition domains, found in several regulatory proteins, that mediate protein–protein interactions. In Kinesin-3s, the FHA domain provides structural support, as well as mediating cargo interactions. Cargo binding by KIF13B is regulated by the phosphorylation of T506 in the FHA domain by the cyclin-dependent kinase 5 (Cdk-5), which allows binding of transient receptor potential vanilloid 1 (TRPV1) (Xing et al., 2012). A change in the susceptibility of mice to anthrax lethal toxin was reported as a result of a point mutation in the FHA domain of KIF1C, that is likely to alter the folding, which further highlights the functional importance of the domain (Durocher and Jackson, 2002, Watters et al., 2001).

The C-terminal region is diverse, but several Kinesin-3s contain a lipid-interaction domain (Figure 4.1A). KIF1A and KIF1B have a pleckstrin homology (PH) domain that is important for binding cargo vesicles (Xue et al., 2010). KIF16A contains a StAR-related lipid transfer (START) lipid/sterol-binding domain (Torres et al., 2011), whereas KIF16B contains a phosphoinositide-binding structural domain (PX), which is involved in the trafficking of early endosomes (Blatner et al., 2007, Hoepfner et al., 2005). KIF1C has a proline-rich region in the C-terminal region, which interacts with the cargo adapter protein BICDR1, 14-3-3 proteins and Rab6 (Schlager et al., 2010, Dorner et al., 1999, Lee et al., 2015b). The C-terminal region of KIF13B contains a CAP-Gly domain, and mice expressing a truncated KIF13B, lacking the CAP-Gly domain, exhibit reduced uptake of LRP-1 (LDL receptor-related protein-1) (Mills et al., 2019).

4.3 FUNCTIONAL PROPERTIES

Kinesin-3s are a family of transporters and most of their members are implicated in long-distance cargo transport. In general, dimeric Kinesin-3 motors are highly processive (Table 4.1). This is achieved by the presence of the K-loop and other structural features of the motor domain, which maintain a stable interaction between

TABLE 4.1
Reported Speed and Run Length of Kinesin-3 Motors

	Average speed	Run length	Nature of construct/assay	References
KIF1	1.4 μm/s	3.4 μm	DCVs in neurons	Lipka et al. (2016)
KIF1A	1.2 μm/s		Full-length purified motor, gliding assay	Okada et al. (1995)
	0.65 μm/s	0.44 μm	Full-length motor, SMMA using COS-7 lysates	Hammond et al. (2009)
	1.5 μm/s	2.6 μm	Truncated motor, SMMA using COS-7 lysates	Soppina et al. (2014)
	2.45 μm/s	9.8 μm	Truncated motor, LZ, SMMA using COS-7 lysates	Soppina et al. (2014)
	0.08 μm/s		Truncated motor in COS-7 cells	Lipka et al. (2016)
Unc104	1.6 μm/s	1.5 μm	Truncated motor, LZ, SMMA	Tomishige et al. (2002)
KIF1B	0.17 μm/s		Truncated motor in COS-7 cells	Lipka et al. (2016)
KIF1C	0.28 μm/s		Truncated motor in COS-7 cells	Lipka et al. (2016)
	2.0 μm/s		Truncated motor, gliding assay	Rogers et al. (2001)
	0.45 μm/s	8.6 μm	Full-length purified motor, SMMA	Siddiqui et al. (2019)
	0.73 μm/s	15.8 μm	Full-length purified motor, SMMA	Kendrick et al. (2019)
KIF13A	0.1–0.3 μm/s		Full-length purified motor, gliding assay	Nakagawa et al. (2000)
	1.4 μm/s	10 μm	Truncated motor, SMMA using COS-7 lysates	Soppina et al. (2014)
KIF13B	0.08 μm/s		Truncated motor in COS-7 cells	Lipka et al. (2016)
	1.3 μm/s	10 μm	Truncated motor, SMMA using COS-7 lysates	Soppina et al. (2014)
Khc73	1.5 μm/s	1 μm	Truncated motor SMMA	Huckaba et al. (2011)
KIF16B	0.97 μm/s	9.5 μm	Truncated motor, SMMA using COS-7 lysates	Soppina et al. (2014)
	0.09 μm/s		Truncated motor in COS-7 cells	Lipka et al. (2016)

Note: SMMA, single-molecule motility assay; LZ, dimerised using leucine zipper; DCVs, dense core vesicles labelled with neuropeptide Y; COS-7, immortalised African Green Monkey cells.

the motor domain and the microtubule throughout the ATPase cycle (Atherton et al., 2014, Okada and Hirokawa, 2000, Scarabelli et al., 2015). Full-length KIF1A is monomeric and can generate about 0.15 pN force (Okada et al., 2003) and very slow (0.15 μm/s) plus-end-directed movement along microtubules (Okada and Hirokawa, 1999). When dimerised or acting in teams, Kinesin-3 motors are 100 times faster

and stronger (Okada et al., 2003, 1995, Oriola and Casademunt, 2013). Indeed, full-length KIF1A, dimerised by addition of a leucine zipper, moves with an average speed of 1.3 μm/s and an average run length of 6 μm (Lessard et al., 2019), and dimerised Unc-104 can generate forces of up to 6 pN (Tomishige et al., 2002). Full-length KIF1C forms a natural dimer and has an average speed of 0.5–0.7 μm/s and an average run length of 9–16 μm (Siddiqui et al., 2019, Kendrick et al., 2019). Removal of its autoinhibitory stalk domain results in a hyperactive KIF1C, with an average speed of 1.2 μm/s (Siddiqui et al., 2019), similar to the transport speed of KIF1C-dependent cargo in cells.

4.3.1 Autoinhibition of Kinesin-3 Motors and Their Activation

Two mechanisms for Kinesin-3 motor regulation have been described. Most Kinesin-3s undergo a monomer-to-dimer transition upon cargo binding, but some are autoinhibited dimers, in which the stalk blocks motor activity until a cargo binds and releases the inhibition (Siddiqui and Straube, 2017).

Regulation by monomer-to-dimer switch is mediated by intramolecular interactions between the neck and tail regions, that hold the kinesin in a monomeric, inactive state. Upon cargo binding, the intramolecular interaction between the neck and tail regions is disrupted and these motors dimerise (Soppina et al., 2014, Tomishige et al., 2002, Okada and Hirokawa, 1999). This can be observed for Unc-104 and KIF1A, which are largely inactive in single motility assays, with intermolecular interactions of the neck coil segment regulating the monomer-dimer transition (Hammond et al., 2009, Al-Bassam et al., 2003). Mutations in the first coiled-coil segment of KIF1A also result in activation of the motor in cells (Yue et al., 2013, Huo et al., 2012). In the KIF13 subfamily, neck coil 1 and coiled-coil 1 are important for the regulation of dimerisation, and deletion of a proline residue at the junction of these domains results in processive dimeric motors (Ren et al., 2016, Soppina et al., 2014).

Autoinhibited dimer regulation occurs for Kinesin-3s that are stable dimers. The stalk, usually a region in the middle of the molecule, interacts with the motor domain to form an autoinhibited state. When an adapter protein or cargo binds to the stalk region, the motor is released from this autoinhibited state. For KIF1C, the binding of PTPN21 or Hook3 to the stalk releases the motor domain and activates intracellular transport (Siddiqui et al., 2019). A similar mechanism seems to regulate KIF13B, which is autoinhibited in solution, but active in a gliding assay. This is likely because binding of the C-terminal tail to the surface resembles the cargo-bound state. In cells, KIF13B is activated when its cargo – human discs large (hDlg) tumour suppressor – binds to the stalk domain and relieves inhibition (Yamada et al., 2007). KIF13B is also regulated by phosphorylation at S1381 and S1410 by Par1b/MARK2 (microtubule affinity-regulating kinase). This allows 14-3-3β binding to the stalk and promotes the intramolecular interaction of KIF13B motor and stalk domains. Consequently, KIF13B microtubule binding is impaired, resulting in the dispersal of the motor in the cytoplasm and a reduction in cell protrusion and axon formation (Yoshimura et al., 2010).

KIF16B exhibits a mechanism of autoinhibition whereby the monomeric motor is held in an autoinhibited conformation by intramolecular interactions of the second

and third coiled-coil with the motor domain (Farkhondeh et al., 2015). Using Förster resonance energy transfer (FRET), it was observed that these motors dimerise on the surface of endosomes (Soppina et al., 2014), so that cargo binding both releases the autoinhibition and facilitates dimerisation of the motor.

4.4 PHYSIOLOGICAL ROLES

Cargoes have been identified for most Kinesin-3 family members (Table 4.2, online material). These range from organelles, such as mitochondria, lysosomes and endosomes, to specific proteins, mRNAs and viral particles. Due to their speed and processivity, Kinesin-3 motors are implicated primarily in neuronal transport.

The movement of dense core vesicles in neurons depends on KIF1A and KIF1C and occurs at an average speed of 1.4 μm/s (Lipka et al., 2016). Integrin-containing vesicles are KIF1C-dependent cargoes that reach top speeds of 2 μm/s and move at an average rate of 0.4 μm/s in human retinal pigment epithelial cells (Theisen et al., 2012). In COS-7 cells, using a rapamycin analogue (rapalogue)-inducible peroxisome-trafficking assay, six out of eight kinesin-3 members were found to significantly enhance transport.

In *C. elegans,* the KIF1A orthologue Unc-104 is a neuron-specific fast anterograde transporter of synaptic vesicle precursors (Okada et al., 1995). Unc-104 cargoes include synaptotagmin, synaptophysin and synaptobrevin-1 (Nonet, 1999, Okada et al., 1995).

Other than neurons, KIF1C has been suggested to mediate Golgi-to-endoplasmic reticulum transport (Dorner et al., 1998) and to maintain Golgi structure (Lee et al., 2015b). In migrating cells, KIF1C transports integrins and is responsible for the maintenance of cell tails and the maturation of focal adhesion sites (Theisen et al., 2012). In macrophages and vascular smooth muscle cells, KIF1C contributes to the formation and regulation of actin-rich podosome structures (Efimova et al., 2014, Kopp et al., 2006). Members of the Kinesin-3 family also play a role in cell division. KIF16A enables the formation of a bipolar mitotic spindle by tethering the pericentriolar material (PCM) to the daughter centriole during mitosis, thereby preventing PCM fragmentation (Torres et al., 2011). KIF13A plays a central role in cytokinesis by translocating FYVE-CENT, a component of the cell abscission machinery, to the spindle midzone (Sagona et al., 2010). KIF14 is upregulated during mitosis and localised to the spindle midzone, with its depletion causing cytokinesis failure and cell death (Carleton et al., 2006). In *Ustilago maydis*, deletion of the sole kinesin-3 leads to a cell separation defect (Wedlich-Soldner, 2002).

The localisation of vesicles is largely controlled by members of the Rab family of GTPases (Zerial and McBride, 2001), and Kinesin-3 members interact with many different Rabs. KIF1A and KIF1Bβ transport Rab3, a synaptic vesicle protein that controls exocytosis of synaptic vesicles along the axon. KIF1C interacts with Rab6 at two sites. Rab6 binding to the motor domain disrupts the motor–microtubule interaction (Lee et al., 2015b), whereas binding to the C-terminus is proposed to mediate cargo loading and subsequent activation. KIF1C also transports Rab11-positive vesicles for the recycling of integrins (Theisen et al., 2012), but the role of Rab11 in controlling the activity of KIF1C remains to be understood. Another

motor protein that binds Rab11-positive vesicles is KIF13A, that controls endosomal sorting and recycling of Rab11-positive endosomal cargo (Delevoye et al., 2014). KIF13A and KIF13B were also identified as interacting partners for Rab10 and the Rab10–KIF13 complex was implicated in the formation of tubular endosomes (Etoh and Fukuda, 2019). This suggests that the KIF13 motors might be able to interact with several Rabs to mediate consecutive steps of cargo sorting, endosome biogenesis and transport.

In non-neuronal cells, KIF16B transports Rab5-positive early endosomes and Rab14-positive vesicles (Hoepfner et al., 2005, Ueno et al., 2011).

An emerging field in Kinesin-3 biology is their cooperation with dynein in bidirectional cargo transport. KIF1C is activated by the cargo adapter Hook3 (Siddiqui et al., 2019) and also interacts with BICDR-1 via its proline-rich tail region (Schlager et al., 2010). Both Hook3 and BICDR-1 are activators of the minus-end-directed motor dynein, and Hook3 can bind simultaneously to KIF1C and dynein (Redwine et al., 2017, Urnavicius et al., 2018, Kendrick et al., 2019). The possibility of complexes containing opposite-polarity motors opens interesting new possibilities in the regulation of Kinesin-3 activity.

It is becoming clear that no typical mechanism for regulating Kinesin-3 motor activity exists and each motor–cargo combination needs to be studied separately to understand how loading of a specific cargo modulates motor activity and thereby determines its cellular distribution.

4.4.1 Preference for Subsets of Microtubule Tracks

Tubulin undergoes a diverse range of post-translational modifications, usually after it polymerises into microtubules. These modifications occur predominantly on the C-terminal tails of both α- and β-tubulin (Magiera and Janke, 2014). The affinity of motors for microtubules can be altered by these modifications, ultimately acting as guides for motor transport (Janke, 2014). The Kinesin-3 family-specific K-loop is proposed to interact with the C-terminal tail (CTT) of β-tubulin, so it is expected that changes in this region would impact Kinesin-3 binding. In ROSA22 mice, knockdown of the polyglutamylase PGs1 resulted in reduced localisation of KIF1A to neurites (Ikegami et al., 2007). Single-molecule imaging of dimerised full-length KIF1A implicates the K-loop in engaging with polyglutamylated CTTs during pause events, thereby linking several processive runs and resulting in the super-processive behaviour typical of Kinesin-3s (Lessard et al., 2019). However, some reports suggest that KIF1A and KIF1Bβ drive lysosomal transport preferentially along tyrosinated (i.e. non-modified) microtubules (Guardia et al., 2016) and that the tubulin deglutamylase CCPP-1 positively regulates the ciliary localisation of *C. elegans* KLP-6 (O'Hagan et al., 2011). In primary human macrophages, the peripheral localisation of KIF1C is negatively regulated by acetylation (Bhuwania et al., 2014), suggesting that acetylation reduces motor activity. For the fungal Kinesin-3 UncA, the tail is necessary and sufficient to guide the motor to selectively recognise detyrosinated microtubules (Zekert and Fischer, 2009; Seidel et al., 2012). These data suggest that most Kinesin-3s recognise post-translational tubulin modifications.

Kinesin-3 interaction with microtubules can also be regulated via the presence of other microtubule-associated proteins (MAPs). MAP7 and Tau have been shown to negatively regulate KIF1A activity, observed as a reduction in the landing rate in the presence of MAP7 or Tau proteins (Monroy et al., 2018). MAP9 was shown to promote KIF1A motility by interacting with the K-loop of KIF1A, mediated by a transient ionic interaction (Monroy et al., 2019). MAP2 localises to the dendrites and an initial segment of the axon, promoting Kinesin-3 (KIF1) cargo transport and slowing down Kinesin-1 (KIF5) transport into axons (Gumy et al., 2017).

4.5 INVOLVEMENT IN DISEASE

Mutations identified in Kinesin-3 family members cause hereditary spastic paraplegia (HSP) and related disorders, such as type 2 hereditary sensory and autonomic neuropathy (HSAN2) and progressive encephalopathy with oedema, hypsarrhythmia and optic atrophy (PEHO) syndrome (Gabrych et al., 2019).

HSP is classified into pure (uncomplicated) or complicated forms, based on the presence or absence of additional neurological defects (Harding, 1993, Fink, 2003). It was recently proposed that manifestation of HSP as a pure or complicated form depends on whether the mutation results in gain of function (i.e. motor becomes hyperactive) or loss of function (i.e. motor becomes weak) (Chiba et al., 2019). Since Kinesin-3 motors are implicated in long-distance transport, their disruption would be expected to most affect the longest cells in the body, i.e. sensory and motor neurons in the sciatic nerve. This might explain why the lower limbs are preferentially affected in these patients.

A homozygous mutation in the gene encoding the highly conserved motor domain of KIF1A was identified in a Palestinian family, presenting with early childhood onset resulting in spastic paraplegia (SPG) 30 (Erlich et al., 2011). Additional mutations were shown by exome sequencing along the regulatory and cargo-binding regions in several families to cause HSAN2 (Riviere et al., 2011), SPG 30 (Klebe et al., 2006, Klebe et al., 2012) or PEHO syndrome (Langlois et al., 2016). In cases where the mutation is heterozygous, it manifests as a non-syndromic intellectual disability (mental retardation, autosomal dominant 9: MRD9) with cerebellar atrophy and axonal neuropathy (Hamdan et al., 2011, Ohba et al., 2015, Yoshikawa et al., 2019). Interestingly, mutations T99M and E253K responsible for SPG 30 are also implicated in PEHO syndrome (Samanta and Gokden, 2019, Esmaeeli Nieh et al., 2015, Lee et al., 2015a). *In vitro,* these two mutations resulted in non-motility in gliding assays, failing to localise to peripheral regions of cultured hippocampal neurons and accumulation in proximal axon regions instead (Esmaeeli Nieh et al., 2015, Cheon et al., 2017). Other KIF1A mutations tested *in vitro*, such as V8M, suggest that an over-activation of the motor results in gain-of-function mutations, leading to pure SPG (Chiba et al., 2019).

For KIF1C, mutations identified in two different families resulted in a novel complicated form of SPG 58, which presented with cerebellar ataxia and pyramidal tract dysfunction (Dor et al., 2014, Caballero Oteyza et al., 2014). Additional mutations, causing either KIF1C truncated at the stalk region or nonsense-degradation, have also been identified (Yucel-Yilmaz et al., 2018, Marchionni et al., 2019). A

homozygous single nucleotide polymorphism in bovine KIF1C results in loss of protein and causes progressive ataxia in Charolais cattle (Duchesne et al., 2018). Interestingly, this KIF1C mutation is correlated with desirable traits in this cattle breed. A slightly better muscular and skeletal development and higher weight of heterozygote carriers of the KIF1C mutation explains why the incidence of the mutation has been maintained at a high frequency in this breed (Duchesne et al., 2018).

A list of known disease-causing mutations in Kinesin-3s is available in online downloadable material (Table 4.3).

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Table 4.2: Cargos identified for Kinesin-3s

Motor	Cargo	Cell type	Reference
KIF1A	Tyrosine kinase A receptor (TrkA)	Mouse dorsal root ganglion neurons	(Tanaka et al., 2016)
	Synaptotagmin and synaptophysin	Rat spinal nerves (cauda equina)	(Okada et al., 1995)
	Dense core vesicles (DCVs)	Rat primary hippocampal neurons	(Lo et al., 2011)
	Beta secretase-1 (BACE-1)	Mouse SCG neurons	(Hung and Coleman, 2016)
	AMPA receptors	Rat brain	(Shin et al., 2003)
KIF1B	mitochondria	Mouse Neuro2a cells	(Nangaku et al., 1994)
	SCG10 / Stathmin-2	Sensory axons in zebrafish	(Drerup et al., 2016)
	Lysosomes	Cos7 african green monkey fibroblast cells	(Matsushita et al., 2004)
	myelin basic protein mRNA	Oligodendrocytes	(Lyons et al., 2009)
	calmodulin mRNA	Spinal motor neurons and cortical neurons	(Charalambous et al., 2013)
KIF1C	$\alpha 5\beta 1$-integrin	RPE1 human epithelial cell line	(Theisen et al., 2012)
	Dense core vesicles (DCVs)	Hippocampal neurons	(Lipka et al., 2016)
	PTPN21/PTPD1	In vitro reconstitution with purified KIF1C	(Siddiqui et al., 2019)
KIF13A	Serotonin type 1A receptor	Mouse hippocampal neurons	(Zhou et al., 2013)
	Viral matrix proteins	Huh7 human hepatoma cell line	(Fehling et al., 2013)
	Viral ribonucleoproteins	A549 alveolar basal cells	(Ramos-Nascimento et al., 2017)
	Mannose-6-phosphate receptors (MPRs)	MDCK canine epithelial cell line	(Nakagawa et al., 2000)
	FYVE-CENT	HeLa human cervical cancer cell line	(Sagona et al., 2010)

KIF13B	Human discs large (hDlg) tumour suppressor	In vitro reconstitution with purified human KIF13B	(Yamada et al., 2007)
	PtdIns(3,4,5)P_3-containing vesicles	Rat PC12 cells and in vitro reconstitution	(Horiguchi et al., 2006)
	Vascular endothelial growth factor receptor 2 (VEGFR2)	Human umbilical vein endothelial cells (HUVECs)	(Yamada et al., 2014)
	Transient receptor potential vanilloid 1 (TRPV1)	CHO cells, rat dorsal root ganglion neurons	(Xing et al., 2012)
KIF16B	Fibroblast growth factor receptor (FGFR)	Mouse embryonic stem cells	(Ueno et al., 2011)
	Transferrin receptor (TfR)	MDCK cells	(Perez Bay et al., 2013)
Kin3	Early endosomes	Ustilago maydis	(Wedlich-Soldner et al., 2002)
	mRNPs	Ustilago maydis	(Baumann et al., 2012)
Nkin2 / Nkin3	Mitochondria	Neurospora crassa	(Fuchs, 2004)
	Early endosomes	Neurospora crassa	(Seidel et al., 2013)
UncA	Early endosomes	Aspergillus nidulans	(Zekert and Fischer, 2009)
Unc-104	presynaptic vesicles	Caenorhabditis elegans	(Hall and Hedgecock, 1991)
	synaptobrevin-1	Caenorhabditis elegans	(Nonet, 1999)
KLP-6	mitochondria	Caenorhabditis elegans Neuro2 cells	(Tanaka et al., 2011)
	polycystins LOV-1 and PKD-2	Caenorhabditis elegans	(Peden and Barr, 2005)
KLP-4	GLR-1 glutamate receptors	Caenorhabditis elegans	(Monteiro et al., 2012)

Table 4.3: List of disease-causing mutations in Kinesin-3s

Motor	Mutation	Inheritance	Reference
KIF1A (SPG 30)	V8M	Dominant - Uncomplicated	(Iqbal et al., 2017)
	I27T	Dominant - Uncomplicated	(Iqbal et al., 2017)
	S58L	Dominant - Complicated	(Lee et al., 2015a)
	S69L	Dominant - Uncomplicated	(Roda et al., 2017, Ylikallio et al., 2015)
	Y74C	Dominant - Uncomplicated	(van de Warrenburg et al., 2016)
	A85D	Dominant - Complicated	(Yoshikawa et al., 2019)
	T99M	Dominant - Complicated	(Lee et al., 2015a)
	G102S	Dominant - Complicated	(Citterio et al., 2015)
	G102D	Dominant - Complicated	(Lee et al., 2015a)
	V144F	Dominant - Complicated	(Lee et al., 2015a, Hartley et al., 2018)
	R167C	Dominant - Complicated	(Hotchkiss et al., 2016)
	G199R	Dominant - Complicated	(Hotchkiss et al., 2016)
	E253K	Dominant - Complicated	(Lee et al., 2015a)
	A255V	Recessive - Uncomplicated	(Erlich et al., 2011)
	R307Q	Dominant - Complicated	(Ohba et al., 2015)
	R350G	Recessive - Complicated	(Esmaeeli Nieh et al., 2015)
KIF1C (SPG 58)	G102A	Recessive - Complicated	(Caballero Oteyza et al., 2014)
	P176L	Recessive - Complicated	(Caballero Oteyza et al., 2014)
	R169W	Recessive - Complicated	(Dor et al., 2014)
	R731X - Termination	Recessive – Uncomplicated	(Novarino et al., 2014)
	Del – Absence of transcript	Recessive - Complicated	(Novarino et al., 2014)
	G>A - Splice site, skipping exon 4	Recessive - Complicated	(Novarino et al., 2014)
Bovine KIF1C	R203Q and skipping of exon 5	Recessive (results in loss of transcript and protein)	(Duchesne et al., 2018)