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One gene, many phenotypes: the role of *KIF5A* in neurodegenerative and neurodevelopmental diseases

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Abstract

Kinesin family member 5 A (KIF5A) is a neuron-specific molecular motor involved in anterograde transport. KIF5A mediates a wide range of trafficking processes that are only partially shared with the other members of the KIF5 family. Since 2002, several disease-causing mutations have been found in the *KIF5A* gene and a link between the specific domain in the encoded protein affected by mutations and the associated phenotype has become evident. Point mutations targeting KIF5A motor and stalk domains, that are expected to impair KIF5A motility, mainly associate with spastic paraplegia type 10 (SPG10) and axonal Charcot-Marie-Tooth (CMT) disease. Oppositely, translational frameshifts causing the elongation of KIF5A tail enhance KIF5A migration towards cell periphery, induce kinesin aggregation, and are linked to amyotrophic lateral sclerosis (ALS) or neonatal intractable myoclonus (NEIMY). This review correlates KIF5A structure and roles in neuronal trafficking with its involvement in the above-mentioned neurodegenerative and neurodevelopmental conditions.

Keywords KIF5A, Hereditary spastic paraplegia, Charcot-Marie-Tooth disease, Amyotrophic lateral sclerosis, Neonatal intractable myoclonus

Background

Neurons are highly polarised cells that strongly rely on intracellular transport to develop and maintain their morphology and functions. Three classes of molecular motors mediate neuronal trafficking along cytoskeletal tracks: the microtubule-based kinesins and dyneins, and the actin-based myosins. Kinesins are mainly anterograde motors transporting cargo towards the plus-end of microtubule tracks, while dyneins are retrograde motors moving in the opposite direction. The main roles played by kinesins and dyneins in neurons are in the axonal or dendritic transport of proteins, vesicles, and organelles. On the other hand, neuronal myosins mediate actin cytoskeleton rearrangements and cargo transport, participating in membrane trafficking, signal transduction processes, and cell movement [1].

In this review, we will mainly focus on a neuron-specific member of the large family of kinesins, the kinesin family member 5 A (KIF5A). Kinesins of the KIF5

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subgroup were the first microtubule-based anterograde motors to be isolated in 1985 from bovine brain and squid axoplasm [2, 3]. Initially considered a single molecular motor, KIF5s were later demonstrated to consist of three highly similar protein isoforms in mammals [4, 5]: KIF5B, which is ubiquitously expressed, and KIF5A and KIF5C, which are only expressed in neurons [6]. The roles of KIF5s in neuronal transport are conserved from *Drosophila* to mammals [7]. In axons, KIF5s take part in the fast transport (50–200 mm/day) of organelles and vesicles and the slow transport (0.1–3 mm/day) of cytoskeletal proteins such as neurofilaments (NFs) and tubulin dimers [8]. In dendrites, kinesins are mainly involved in the trafficking of vesicles, proteins, and RNA granules required for synaptic transmission [1]. Although all three KIF5s are expressed in the brain, only KIF5A has been reported to be affected by mutations that cause neurodegenerative or neurodevelopmental disorders [9]. In the next paragraphs, we will correlate KIF5A structure and roles in neuronal trafficking with its involvement in disease.

KIF5A structure and regulation

KIF5A is a 1,032-amino acid protein encoded by the 29-exon *KIF5A* gene, located on chromosome 12q13.3 [4]. KIF5A is highly homologous to KIF5B and KIF5C, but it is the longest protein in the KIF5 subfamily, having 73 unique amino acids in its C-terminal tail [10], which confer to KIF5A the ability to bind cargoes that cannot interact with KIF5B and KIF5C [11]. All three KIF5 conventional kinesins comprise a globular motor domain, a coiled-coil stalk, and a tail region [12] (Fig. 1). The motor domain, also called head, is required for microtubule binding and ATP hydrolysis. The stalk domain mediates kinesin dimerization and conformational changes, whereas the tail is involved in cargo and/or adaptor binding [10].

KIF5 head contains a microtubule-binding site showing higher affinity for axonal compared to dendritic microtubules. This differential affinity is essential to promote the specification of a single axon from multiple neurites during neurogenesis, since KIF5-dependent transport will mainly occur along a single neuronal protrusion. The preferential recruitment of KIF5s to axons depends on the different microtubule stabilities between the proximal axon and dendrites. Coherently, when microtubule dynamics are perturbed during neuronal development, neuronal polarity is disrupted [13, 14].

The stalk domain of the KIF5 motors is formed of a series of coiled-coil structures through which KIF5s associate into homodimers [15]. About half of the homodimers found in cells interacts with two kinesin light chain

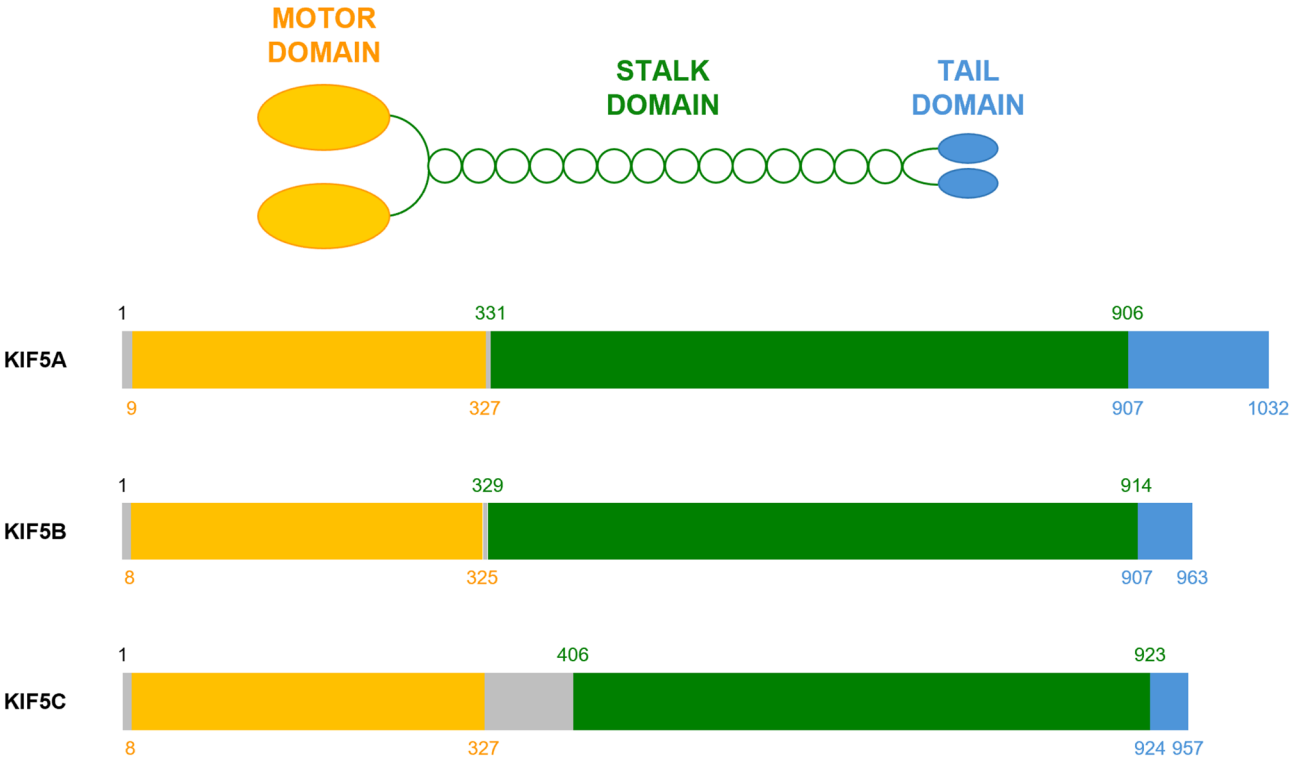

Fig. 1 Comparison of KIF5A, KIF5B, and KIF5C protein structures divided into the three main functional domains of conventional kinesins (motor, stalk, and tail domains). The three KIF5 isoforms are highly similar, but KIF5A has the longest tail domain, with 73 unique amino acids in its C-terminal region, making it capable to uniquely bind to specific cargoes

(KLC) molecules, forming tetrameric holoproteins. Binding occurs between the N-terminus of KLCs and a KIF5 region spanning across the stalk and tail domains [16, 17]. KIF5s can bind cargo either directly through the portion of their tail downstream of the KLC binding region [18], or indirectly through adaptors like KLCs. KLCs exist in four different isoforms (KLC1-4) produced by alternative splicing in their C-terminal tetratricopeptide repeat domain, providing the specificity in cargo binding [19, 20].

In the absence of cargo, KIF5s undergo autoinhibition, a process through which the tail domain folds onto the head to block the ATP cycle required to fuel transport. This head-to-tail interaction is guided by the isoleucine-alanine-lysine (IAK) motif in the C-terminal region of KIF5s. Autoinhibition is a key mechanism preventing unnecessary ATP-wasting movements of empty KIF5 motors in the absence of cargo. Consistently, deletion or mutation of the IAK motif result in constitutively active KIF5 motors. Upon interaction with adaptors or cargoes, KIF5 autoinhibition ceases and the motor domain contacts microtubules to begin transport [21, 22].

KIF5 movement is also regulated by phosphorylation. Indeed, glycogen synthase kinase 3β (GSK3β) blocks KIF5-mediated anterograde trafficking by phosphorylating KLC2, while KIF5 head phosphorylation by p38 mitogen-activated protein kinase (MAPK) or MAPK10 inhibits microtubule binding [6].

KIF5A cargoes shared with the other conventional kinesins

KIF5s participate in a wide variety of transport processes in neurons. The central role of KIF5s in axonal trafficking is well illustrated by the finding that loss-of-function (LOF) mutations of the KIF5 homologous in *Drosophila*, kinesin heavy chain (*Khc*), cause the accumulation of organelles and vesicles along axons, obstructing bidirectional transport and ultimately leading to motor neuron degeneration and premature death of the affected flies. Conversely, *Khc* haploinsufficiency is well tolerated in *Drosophila* [23, 24].

Regarding fast anterograde trafficking, KIF5s transport vesicles containing presynaptic membrane proteins that guide the fusion of synaptic vesicles with the plasma membrane; these proteins include syntaxin and some components of the synaptosome-associated protein (SNAP) complex and its receptor (SNARE), as SNAP23, SNAP25, synaptotagmin, and synaptobrevin [25, 26]. SNAP25 can directly bind to the KIF5 tail [27], while syntaxin acts as a bridge between KIF5 and the proteins hosted into presynaptic vesicles. The syntaxin-syntabulin-KIF5 complex has been identified as a key player in the assembly of presynaptic terminals in the developing hippocampus [28, 29]. Additional vesicular cargoes specifically transported by KIF5s in association with KLCs include vesicles harbouring phosphorylated amyloid precursor protein or receptors for LDL receptor related protein 8 (LRP8/APOER2) [30, 31]. KIF5s also participate in the fast transport of mitochondria, which requires either syntabulin and RAN binding protein 2 (RANBP2) or trafficking kinesin proteins 1 and 2 (TRAK1/2 or Milton) and Ras homology family member T1 and 2 (RHOT1/2 or Miro) to be linked to KIF5 motors [32–35]. Even in the case of mitochondrial trafficking, KIF5s play a central role, as shown by knock-out (KO) animal models. For instance, *Kif5b* loss in mice leads to a perinuclear accumulation of mitochondria in cells which can be restored by the exogenous expression of any human KIF5 [5, 36]. A similar phenotype characterises *Kif5a* KO animal models [37, 38]. Concerning neurons, the regulation of bidirectional mitochondrial trafficking along axons is finely tuned by the adaptors TRAK1/2, which coordinate the formation of a protein complex that can link mitochondria to both dynein and KIF5s [39]. Moreover, mitochondrial transport in neurons critically relies on the integrity of microtubule-based bidirectional trafficking. In fact, the individual depletion of dynein, dynactin, or KIF5s is sufficient to disrupt mitochondrial motility in both directions [40–42]. Finally, KIF5 motors are required for endolysosomal transport. Both lysosomes and early endosomes labelled with Ras oncogene family members 4 and 5 (RAB4/5) are transported by KIF5s [43–45]. More in detail, lysosomes are transported by both KIF5B, since its silencing precludes lysosome dispersion upon cytoplasm acidification [36], and KIF5A, since lysosome accumulation occurs in neurons when KIF5A is pharmacologically blocked by the neurotoxic compound trimethyltin chloride [46].

Another key process involving KIF5s is the slow anterograde trafficking of proteins in neurons. Concerning cytoskeletal proteins, both NFs and tubulin dimers are among KIF5 protein cargoes [47]. The trafficking of tubulin dimers requires the presence of either KLC or dihydropyrimidinase like 2 (DPYSL2/CRMP2) as adaptors [48]. Such transport process is crucial for axonal specification and outgrowth during mammalian development [49]. Indeed, *Kif5* knock-down (KD) in rat hippocampal neurons decreases neurite length and prevents the transport of synapsin and growth associated protein 43 (GAP43) to neurite tips [50]. Additionally, KIF5s are responsible for the anterograde trafficking of dynein to microtubule plus-ends, which is essential to allow dynein-mediated retrograde transport; this further highlights the interdependence between KIF5 motors and dynein [51].

KIF5s also participate in dendritic trafficking. For instance, they transport glutamate receptor-interacting protein 1 (GRIP1), an adaptor for the α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor

(AMPAR) subunit glutamate receptor 2 (GluR2). Binding to the GRIP1-GluR2 complex drives KIF5s from axons to dendrites. In addition, overexpression of a dominant-negative headless KIF5 construct in cultured neurons was shown to cause a drastic reduction in GluR2 clustering in dendrites, underlining the essential role played by KIF5 motors in GluR2 trafficking [52]. KIF5s also bind directly to huntingtin-associated protein 1 (HAP1) for the dendritic transport of γ-aminobutyric acid (GABA) type A receptors ($GABA_A$Rs) [53]. Finally, KIF5 motors take part in the dendritic transport of RNA granules. The mRNA species that can be found in these granules encode factors involved in synaptic plasticity, and they associate with at least 42 proteins [54, 55]. KLCs are not required for the KIF5-mediated trafficking of RNA granules [56].

KIF5A-specific cargoes

Although several KIF5A cargoes are shared with KIF5B and KIF5C, observations made in KO animal models suggest that KIF5A plays unique roles in neuronal trafficking (Fig. 2). Indeed, constitutive *Kif5a* KO mice develop normally and do not display abnormal brain morphology but die soon after birth due to unexpanded lungs and respiratory failure [37, 47], suggesting that KIF5A activity is central to the postnatal functioning of neurons [57]. Primary motor neurons extracted from the same *Kif5a* KO mice also exhibit reduced survival and neurite outgrowth in vitro. Neuron-specific *Kif5a* loss, on the other hand, causes the insurgence of seizures and the rapid degeneration of large-calibre axons, resulting in progressive hindlimb paralysis and death within a few weeks [11, 37, 47]. Finally, partial or complete *Kif5a* loss in retinal ganglion cells of adult mice causes their degeneration even in the absence of damage due to the impaired trafficking of mitochondria and proteins involved in neuronal maintenance along the optic nerve [58]. Of note, *KIF5A* depletion is not compensated by mechanisms involving KIF5B or KIF5C [57], and *Kif5a* haploinsufficiency is not associated with any motor deficits both in vivo and in vitro [37, 47], similarly to *Khc* KO in *Drosophila*.

One of the earliest pieces of evidence for a KIF5A-specific role in axonal transport came from Xia and colleagues [47], who observed accumulation of NFs in the neuronal cell bodies in dorsal root ganglia of conditional *Kif5a* KO mice. Such accumulation resulted from a strong decrease in the anterograde transport frequency of NFs, that was only partially restored by *Kif5b* or *Kif5c* overexpression [47, 59]. However, more recent studies on both human embryonic stem cell (hESC)-derived motor neurons and animal models deprived of KIF5A did not find any alterations in NF distribution or transport [11, 38, 57]. The potential involvement of KIF5A in the maintenance of cytoskeletal integrity and neurite outgrowth was anyways confirmed. Indeed, motor neurons differentiated from *KIF5A* KO hESCs display shorter and less branched neurites compared to wild-type (WT) motor neurons after two weeks in culture, although this difference becomes less evident with time. Moreover, hESC-derived motor neurons deprived of KIF5A exhibit defects in recovering after axotomy independently of the

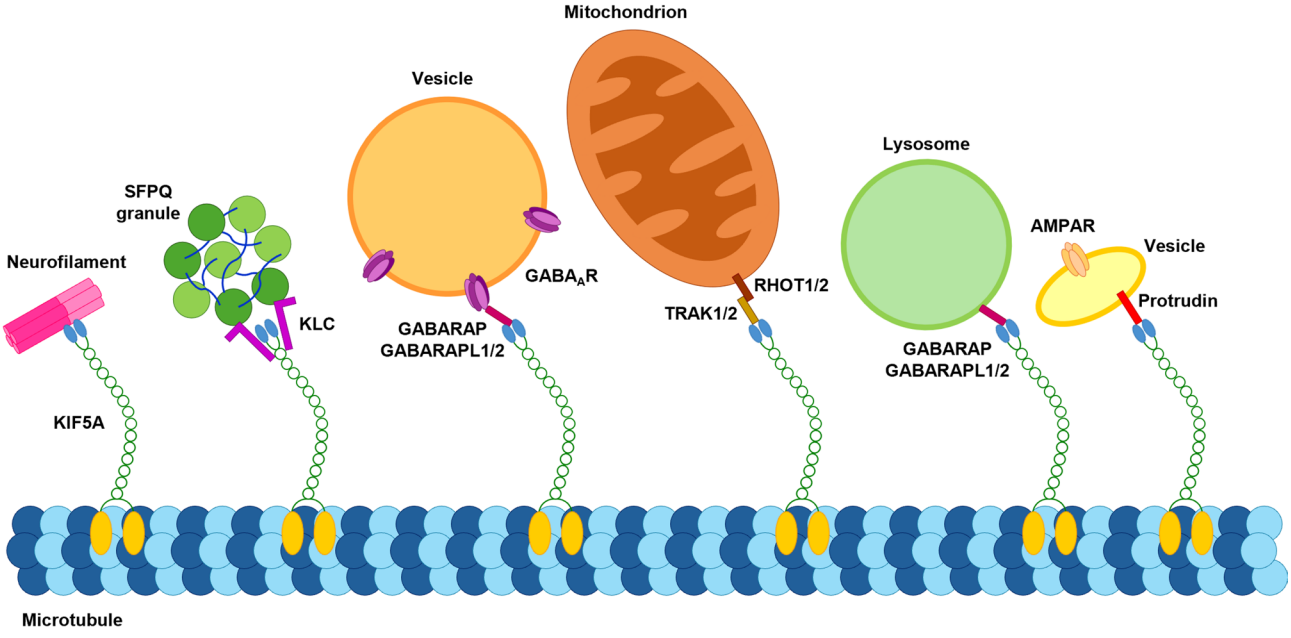

Fig. 2 KIF5A is involved in the anterograde transport of cytoskeletal proteins (e.g. neurofilament), RNA granules (e.g. SFPQ-containing ribonucleoprotein granules), vesicles (e.g. neurotransmitter receptor carriers), and organelles (e.g. mitochondria and lysosomes) along microtubules in either axons or dendrites

culturing period, highlighting the involvement of KIF5A in axonal regeneration [57].

KIF5A also has a key role in mitochondrial trafficking, although other kinesins can interact with these organelles (e.g. KIF5B and KIF1B [40, 60]). Indeed, *Kif5a* KO was shown to impair the bidirectional transport of mitochondria in murine motor neurons, leading to disrupted axonal morphology and reduced cell survival. Additionally, the decrease of axonal mitochondria caused by *kif5Aa* truncation in zebrafish resulted in the degeneration of peripheral sensory neurons [37, 38]. A defect in the anterograde transport of mitochondria was also observed in *Kif5a* KD retinal ganglion cells [61] and in *KIF5A* KO hESC-derived motor neurons kept in culture for 42 days, which suggests that this dysfunction could be progressive [57].

The specificity of some KIF5A roles among conventional kinesins is also supported by the observation that *KLC1* KO causes the accumulation of KIF5A, but not KIF5B or KIF5C, in the distal Golgi [62]. An example of cargo known to be preferentially transported by KIF5A in association with KLC1 is the ribonucleoprotein granule harbouring splicing factor proline/glutamine-rich (SFPQ) [55, 63]. Indeed, SFPQ was shown to mediate the interaction between neurotrophin-regulated transcripts and the KIF5A-KLC1 tetramer to drive them to motor and sensory axons for local translation [64, 65]. The specificity of the interaction between SFPQ and the KIF5A-KLC1 complex is provided by the amino acid sequence unique to the KIF5A tail domain among KIF5s. Of note, the overexpression of the disease-linked p.R280H KIF5A mutant in murine dorsal root ganglion neurons in vitro prevented the transport of SFPQ granules to axons, although mitochondrial trafficking remained unaltered [63]. A similar time-dependent result was obtained in *KIF5A* KO hESC-derived motor neurons cultured for 42 days [57].

Another trafficking process for which KIF5A is essential involves neurotransmitter receptors. Nakajima et al. [11]. proved that the epileptic seizures affecting newborn mice after the neuron-specific depletion of *Kif5a* are caused by a reduction of the membrane exposure of $GABA_A$Rs in the hippocampus resulting from a decrease in their anterograde movement. The same finding was obtained upon *Kif5a* KD in WT animals, and the defect was rescued by the overexpression of *Kif5a*, but not *Kif5b* or *Kif5c*. The interaction between KIF5A and $GABA_A$Rs is mediated by the adaptor molecules $GABA_A$R-associated protein (GABARAP) or $GABA_A$R-associated protein-like 1 and 2 (GABARAPL1/2), which bind to the 73-amino acid sequence specific to KIF5A tail among KIF5s. Consistently, murine hippocampal neurons deprived of *Kif5a* displayed accumulation of GABARAP-positive vesicles within proximal dendrites and reduced number, size, and anterograde trafficking of $GABA_A$R-positive vesicles. A coherent observation was made upon *kif5Aa* truncation in zebrafish, which led to motor neuron hyperexcitability and muscle spasticity [38], highlighting that the role played by KIF5A in the trafficking of synaptic components is evolutionarily conserved. KIF5A is also essential for the activity-dependent internalisation of hippocampal AMPARs upon *N*-methyl-*D*-aspartate (NMDA)-mediated activation, a key step in long-term synaptic depression [66, 67]. KIF5A binding to AMPARs is mediated by the adaptor protein protrudin. KO or expression of dominant-negative forms of either KIF5A or protrudin is sufficient to abolish the uptake of AMPARs upon NMDA signalling, although KIF5A role in the process is partially overlapping with KIF5C [67].

Finally, KIF5A has a central role in lysosomal transport. In fact, the decrease in KIF5A protein levels observed in N2a cells treated with the neurotoxic agent trimethyltin chloride led to the accumulation of dysfunctional lysosomes as a consequence of their diminished anterograde trafficking, which is mediated by KIF5A in complex with GABARAP or GABARAPL1/2. Notably, *Kif5a* overexpression in trimethyltin chloride-treated N2a cells and murine hippocampal neurons rescued the altered lysosomal distribution and degradative capacity [46].

KIF5A-related diseases

Since the identification of the first disease-causing *KIF5A* mutation in 2002, many other variants have been found in the *KIF5A* gene (Fig. 3 and Supplementary Table). Most mutations targeting *KIF5A* are linked to neurodegenerative diseases, a heterogeneous group of genetic or sporadic disorders characterised by the progressive degeneration of specific neuronal populations. Mutations in *KIF5A* underpin three different and currently incurable neurodegenerative conditions: spastic paraplegia type 10 (SPG10), an axonal form of Charcot-Marie-Tooth (CMT) disease, and amyotrophic lateral sclerosis (ALS). Besides neurodegeneration, mutations in *KIF5A* are also associated with a rare and severe neurodevelopmental condition named neonatal intractable myoclonus (NEIMY).

Notably, *KIF5A* mutations linked to distinct diseases tend to cluster in different domains of the corresponding protein. Specifically, SPG10 and *KIF5A*-related CMT are caused by point mutations affecting the head and stalk domains [68, 69], while *KIF5A*-associated ALS and NEIMY are caused by frameshift mutations in the tail domain [70, 71].

Spastic paraplegia type 10

SPGs are a heterogeneous group of adult-onset neurodegenerative diseases targeting cortical motor neurons with an overall prevalence of 1.8/100,000. SPGs can be

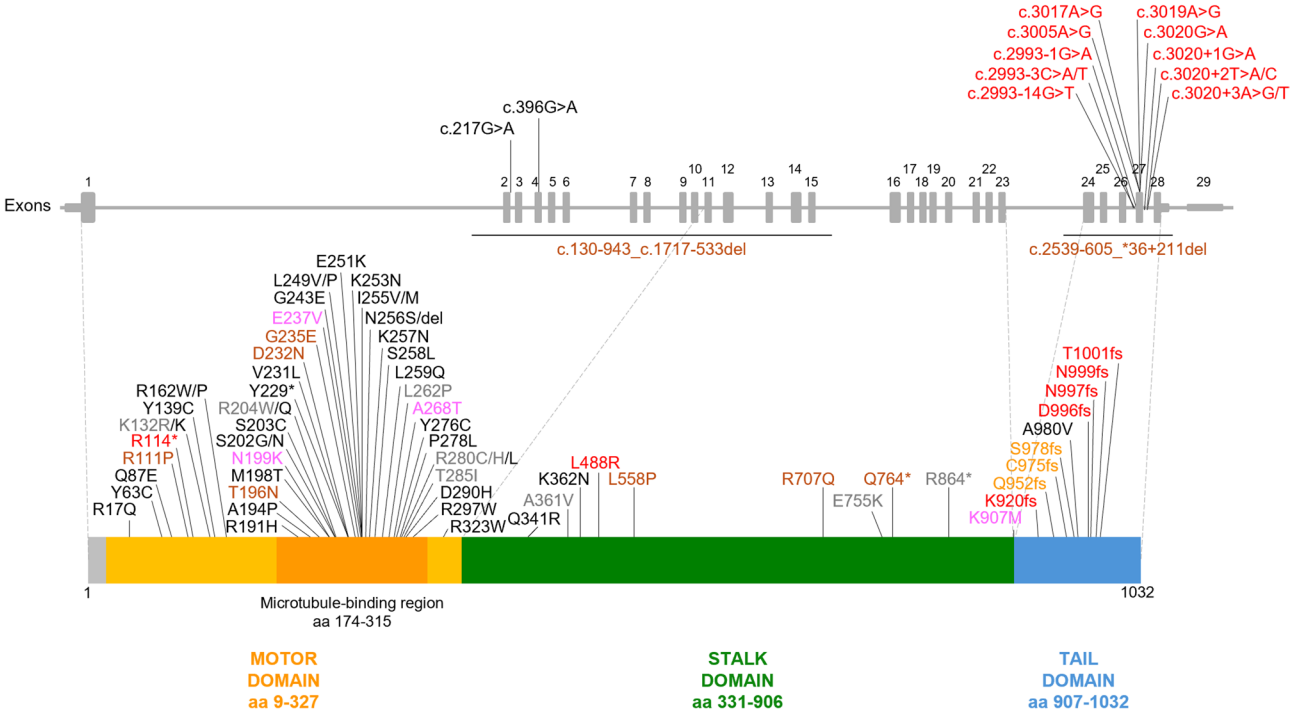

Fig. 3 Distribution of KIF5A pathogenic variants associated with HSP/SPG10 (black), CMT (brown), ALS (red), NEIMY (orange), or other phenotypes (pink). Variants associated with more than one disease are in grey. See the Supplementary Table for further details. Adapted from Cozzi M, Magri S et al. Altered molecular and cellular mechanisms in KIF5A-associated neurodegenerative or neurodevelopmental disorders. *Cell Death Dis* 2024; 15: 692 [83].

distinguished into a pure form and a complicated form based on the symptomatology. Pure SPGs present with slowly progressive lower limb spasticity, asymptomatic upper limb hyperreflexia, brisk jaw jerk, and sensory loss. Complex SPGs can be characterised by ataxia, peripheral neuropathy, extrapyramidal signs, cognitive impairment, and/or epilepsy in addition to leg spasticity [72]. Regarding the molecular bases of SPGs, genes targeted by SPG-related mutations point at impairments in axonal transport and membrane trafficking, myelination defects, mitochondrial dysfunction, and alterations in lipid metabolism as candidate mechanisms underpinning SPG pathogenesis [73, 74].

KIF5A is the locus associated with SPG10, that accounts for around 3% of pure SPG cases and 5–8% of complex SPG cases [75]. This makes *KIF5A* mutations one of the most prevalent causes of the complicated form of the disease [76]. Most *KIF5A* mutations linked to SPG10 cluster in proximity to or within switches 1 and 2, that are part of the γ-phosphate-sensing region of the KIF5A motor domain. During ATP hydrolysis, these switches undergo conformational changes that are essential for KIF5A activity [77] and are lost in the mutant protein. Consistently, Ebbing et al. [78]. demonstrated that the p.K253N, p.N256S, and p.R280C SPG10-KIF5A mutants display a reduced affinity for tubulin compared to the WT protein; moreover, these mutant motors can only move a few steps along microtubules before detachment, suggesting that KIF5A-mediated axonal transport may be disturbed by SPG10-linked mutations [78, 79]. In line with this hypothesis, Wang and colleagues [80] reported that the overexpression of p.N256S KIF5A in mouse cortical neurons led to a decrease in bidirectional NF transport frequency, although distal axons did not appear significantly deprived of NFs. Additionally, a p.N262S Khc *Drosophila* model harbouring the equivalent of the p.N256S KIF5A substitution displayed axonal swellings, aberrant synaptic structure, and increased mortality compared to control flies [81].

The region of the KIF5A head involved in ATP hydrolysis is another hotspot for SPG10 mutations. Even in this case, the affinity of SPG10-KIF5A for microtubules is decreased compared to the WT protein, and this is accompanied by a marked reduction in the basal ATPase rate and/or the microtubule gliding velocity depending on the considered KIF5A mutant [82]. The transmission to the neck and coiled-coil domains of the conformational changes occurring in KIF5A head upon ATP hydrolysis and the dimerization of KIF5A motor domains can be impacted by SPG10-related mutations, too [79]. Moreover, residues that contribute to shape and stabilise the nucleotide-binding pocket in KIF5A motor head can also be targeted in SPG10. Indeed, we recently reported the p.R17Q substitution in KIF5A, that causes a change in steric hindrance within this pocket that is predicted to weaken SPG10-KIF5A ability to bind to ATP. p.R17Q

KIF5A is also affected by a faster proteasome-mediated degradation compared to WT KIF5A [83].

Charcot-marie-tooth disease

CMT is a heterogeneous group of adult-onset hereditary peripheral neuropathies targeting both sensory and motor neurons and represents the most common inherited disease of the peripheral nervous system [84]. In CMT, neurodegeneration is caused by demyelination (CMT1) or axonal degeneration (CMT2), and these two subtypes can be clinically distinguished by nerve biopsy and electrophysiology [85]. CMT symptoms usually start developing during adolescence with foot drop and sensory loss in the lower legs and feet. Motor and sensory degeneration then spreads to the upper limbs, manifesting as hand muscle weakness. Clinical severity is highly variable in CMT even when patients share the underlying genetic cause, suggesting that environmental and susceptibility factors may contribute to neurodegeneration [86, 87]. In the last 30 years, CMT has been linked to more than 80 genes [88]. Based on the roles of the corresponding gene products in neurons, the candidate pathogenic mechanisms in CMT comprise alterations in axonal transport, impaired mitochondrial dynamics and interactions between organelles, and defects in local axonal protein synthesis [89]. *KIF5A* mutations are associated with axonal CMT and appear to be quite rare, even if the partial overlap between complex SPG10 with sensory involvement and CMT symptoms makes it difficult to properly discriminate between the two neurodegenerative diseases.

Few functional analyses of CMT-KIF5A mutants have been performed so far. In one study, Soh and colleagues [90] generated a *C. elegans* model in which the *KIF5A* orthologous gene *unc-116* was inactivated to study the contribution of its LOF to the axonal CMT phenotype. They found that worms deprived of *unc-116* displayed a shorter body length compared to control animals and were debilitated in both swimming and crawling already at the larval stage. These observations correlated with morphological defects of cholinergic axons and skeletal muscles, pointing towards the neuromuscular junction (NMJ) as a primary site of *KIF5A*-linked CMT. On the other hand, we recently investigated the molecular behaviour of the SPG10/CMT-linked p.R864* KIF5A mutant, showing that its tail truncation generates a persistently active KIF5A motor due to loss of autoinhibition. Concomitant with this gain of function (GOF) mechanism is the abolishment of the KIF5A domain mainly involved in cargo binding, which likely leads to a loss of transport competence, as suggested by the poor co-distribution between p.R864* KIF5A and mitochondria [83].

Amyotrophic lateral sclerosis

ALS is a rare, adult-onset neurodegenerative disease in which both cortical and spinal motor neurons are lost, leading to progressive muscular atrophy and death within 3–5 years after the onset of symptoms. Besides motor neurons, also skeletal muscle and glial cells can be directly affected [91, 92]. Moreover, neuronal loss can also occur in the frontotemporal cortex in some ALS forms, causing a mixed pathology clinically characterised by motor neuron disease and frontotemporal dementia [93], commonly referred to as ALS/FTD.

To date, ALS aetiology is still not fully understood, and a combination of genetic and environmental factors is considered to be at the basis of the disease. In fact, only ~ 10% of ALS cases are associated with familial inheritance (fALS), while ~ 90% of cases are sporadic (sALS). fALS and sALS fully overlap in symptomatology, but fALS usually displays a more severe disease progression compared to sALS. Mutations in more than 40 genes have been associated with fALS, but ~ 30% of fALS cases have not yet been linked to any specific gene defect. Based on the functions of ALS-associated gene products, the main pathological mechanisms suspected to be implicated in neurodegeneration include aberrant RNA processing, protein misfolding and aggregation, endoplasmic reticulum stress, mitochondrial dysfunction and oxidative stress, axonal transport impairment, excitotoxicity, and neuroinflammation [94, 95]. Of note, sALS is characterised by abnormal behaviours of some of the proteins that are also affected by fALS-linked mutations, hinting that the pathogenic mechanisms underpinning the two ALS forms are likely partially shared [96].

ALS-linked *KIF5A* mutations were identified in 2018 [70, 71]. The P986L KIF5A substitution, proposed to be a potential risk factor for ALS [70, 71], was recently proven to be non-pathogenic in *Drosophila* [97] but also found to cause a faster disease progression in two cohorts of Italian ALS patients [98]. Instead, pathogenicity was demonstrated for a group of frameshift mutations sharing molecular and functional alterations. Indeed, most ALS-linked translational frameshifts affecting KIF5A lead to tail elongation up to a stop codon 14 amino acids downstream to the WT one. Such frameshifts can be associated or not with the skipping of exon 27 [70, 71]. The aberrant tail produced by ALS-linked variants prevents KIF5A autoinhibition due to the alteration of the charge distribution around the IAK motif spanning KIF5A residues 917–923. This generates a persistently active motor that moves at a faster pace compared to WT KIF5A, with a consequent accumulation of the mutant protein at microtubule plus-ends. There, ALS-KIF5A forms sequestosome 1/p62 (SQSTM1/p62)-positive inclusions that also sequester the WT protein [99, 100], suggesting that an aberrant GOF mechanism takes

place, as frequently occurs in ALS. Of note, ALS-KIF5A aggregates do not contain TAR DNA-binding protein 43 (TDP-43), a DNA/RNA-binding protein that localises to the nucleus in healthy cells but aberrantly translocates to the cytoplasm and forms aggregates in motor neurons in most sALS subtypes and several forms of fALS, depending upon the specific gene involved [101].

Besides SQSTM1/p62 binding, ALS-KIF5A exhibits other aberrant interactions with both proteins and RNA species. For example, several proteins involved in RNA processing show an enhanced interaction with ALS-KIF5A compared to WT KIF5A; conversely, factors involved in protein stabilisation and stress response display a reduced interaction with ALS-KIF5A with respect to the WT protein. Concerning RNA, transcripts that exhibit higher binding to ALS-KIF5A compared to WT KIF5A include nerve growth factor-regulated RNAs, while underrepresented transcripts are involved in synapse and potassium channel assembly. Consistently, RNA sequencing on induced pluripotent stem cell (iPSC)-derived motor neurons confirmed alterations in pathways involved in neurite outgrowth, NMJ function, and mRNA processing in cells harbouring ALS-KIF5A. Regarding the last category, it is also relevant to underline that the presence of ALS-KIF5A in iPSC-derived motor neurons was shown to determine the aberrant splicing of transcripts involved in intracellular transport and cytoskeleton maintenance and to disrupt the gradient of RAN, member Ras oncogene protein (RAN), required to maintain an efficient transport flux between the nucleus and the cytoplasm [99]. In addition, motor neurons harbouring ALS-KIF5A display decreased soma area, axon length, and neurite branching, accompanied by the presence of NF-positive swellings along the axon, and their survival is reduced compared to their WT counterparts [102].

The protein levels of ALS-KIF5A were found reduced compared to WT KIF5A in primary or iPSC-derived motor neurons and in animal models (*C. elegans*, *D. melanogaster*, *M. musculus*) [99, 100, 102–104], despite starting from comparable mRNA levels. We demonstrated that the reduced ALS-KIF5A levels depend on a faster protein turnover mediated by the ubiquitin-proteasome system [83]. Combined with the aggregation propensity of ALS-KIF5A found in both cell and animal models [83, 99, 100, 104, 105] and with its ability to sequester the WT protein, the reduction in ALS-KIF5A protein levels may severely limit the overall amount of KIF5A motors available for transport, thus promoting neurodegeneration.

The ability of ALS-KIF5A to transport cargo is still debated. On one hand, Baron et al. [99] reported that mutant *KIF5A* overexpression determined an increase in the fraction and velocity of anterogradely moving mitochondria in cultured murine motor neurons. Conversely, neither Pant and colleagues nor we [83, 100] observed co-distribution between ALS-KIF5A aggregates and mitochondria, suggesting that mutant KIF5A oligomerisation could lead to a loss of interaction with cargoes. In the latter scenario, soluble ALS-KIF5A homodimers or WT-mutant KIF5A heterodimers could drive the distal accumulation of mitochondria or other KIF5A cargoes due to missing autoinhibition, whereas ALS-KIF5A deposition into poorly dynamic aggregates sequestering the WT protein may oppositely favour an imbalance towards retrograde transport. In these conditions, the equilibrium in axonal trafficking is likely impaired in *KIF5A*-linked ALS.

Animal models have been generated to better understand the role of *KIF5A* frameshift mutations in ALS. For example, *Drosophila* larvae selectively expressing human ALS-KIF5A in motor neurons [104] exhibited impaired locomotion due to posterior leg paralysis; this is a clear sign of axonal degeneration in flies, which is also evidenced by the altered spatial organisation of motor neuron cell bodies in the ventral nerve cord. With development, ALS-KIF5A larvae died more frequently than their WT counterparts, and the few surviving adult flies were defective in climbing and displayed a shorter life expectancy. ALS-KIF5A was found to aggregate in both cell bodies and axons of larval motor neurons and such aberrant distribution correlated with the formation of axonal swellings and the focal accumulation of mitochondria and synaptic vesicles away from the synaptic bouton. The synaptic deprivation of these essential factors determined a reduction in the length and surface of NMJs as well as in the number of active zones, causing a strong alteration in synaptic transmission in both resting and stimulated conditions. On the other hand, a knock-in murine model mimicking ALS-KIF5A generated by Rich and colleagues [103] did not develop an overt ALS phenotype. Both heterozygous and homozygous ALS-KIF5A animals were indeed similar in weight, behaviour, and survival to WT mice. Furthermore, ALS-KIF5A aggregates were not observed in motor neurons. Nevertheless, when ALS-KIF5A animals were subjected to peripheral nerve injury, they exhibited incomplete motor unit recovery. Such defect was accompanied by a reduction in motor neuron and motor fibre size and in NMJ surface ipsilaterally to the injury site despite no evidence of motor neuron loss. Additionally, aged heterozygous ALS-KIF5A mice displayed a lower number of motor units and were even more defective in recovering after peripheral nerve injury compared to WT animals. This mild phenotype can probably be explained by the endogenous expression of ALS-KIF5A in these mice and is indicative of a repair defect that resembles the one observed in KIF5A KO hESC-derived motor neurons [57].

Finally, *KIF5A* can also act as modifier gene in ALS independently of mutations. In a study aimed at

identifying modifier genes influencing astrocyte behaviour in ALS, Szebényi and colleagues [106] showed that KIF5A is expressed in astrocytes, albeit at very low levels. The authors uncovered an unexpected downregulation of KIF5A mRNA and protein levels in SOD1-ALS astrocytes compared to controls by overlapping ALS-related gene networks identified via genome-wide association studies with transcriptomic and proteomic datasets obtained from iPSC-derived astrocytes harbouring mutations in the superoxide dismutase 1 (*SOD1*) gene. *KIF5A* downregulation impaired the growth of SOD1-ALS astrocyte processes, whose distal portions also displayed microtubule disorganisation and were depleted of KIF5A and mitochondria. These phenotypes could be replicated by knocking down *KIF5A* in WT iPSC-derived or primary astrocytes, with no effects on KIF5B or KIF5C levels. Moreover, the overexpression of MAPK8/JNK1, a kinesin regulator, was shown to promote KIF5A motility and rescue the arborisation defects in SOD1-ALS astrocytes.

Neonatal intractable myoclonus

NEIMY is a severe neurological condition manifesting through drug-resistant myoclonic seizures soon after birth, that often cause patients' death in infancy. In addition to myoclonus, NEIMY symptoms include myopathy and hypotonia, pallor of the optic nerve and abnormal eye movements, intermittent apnoea, dysphagia, developmental arrest, and in some cases progressive leukoencephalopathy.

NEIMY was first reported in 2016 and is caused by *de novo* frameshift mutations in *KIF5A* affecting the C-terminal tail of the corresponding protein [107, 108]. Firstly, Duis and colleagues [107] described two single-base deletions in *KIF5A* (c.2854delC and c.2934delG) leading to translational frameshifts (p.Q952Rfs*96 and p.S978Lfs*70, respectively) and protein elongation to a new stop codon 42 bases downstream of the WT one. Then, Rydzanicz et al. [108]. reported a c.2922delC/p.C975Vfs*73 KIF5A mutation (originally referred to as c.2921delC/p.S974fs KIF5A) in a child displaying leukoencephalopathy and myoclonic seizures of potential spinal cord origin. The three NEIMY-KIF5A mutations reported in literature cause a comparable symptomatology and are predicted to share the aberrant frame with ALS-KIF5A. In both clinical reports, mitochondrial dysfunction was hypothesised as the main molecular defect underlying NEIMY pathogenesis. This hypothesis is coherent with the central role played by KIF5A in the axonal trafficking of mitochondria [38] and with the identification of the p.S978fs KIF5A mutation as potential cause of a mitochondrial disease by Da Re et al. [109]. On these bases, Rydzanicz and colleagues [108] speculated that the p.C975Vfs*73 mutation may impair KIF5A ability to interact with the adaptor proteins required for mitochondrial trafficking, such as TRAK2; in fact, TRAK2 interaction with KIF5A is reduced when the kinesin tail is truncated at residue 962 [110]. On the other hand, Duis et al. [107]. hypothesised that NEIMY-related KIF5A variants could exert a dominant-negative effect on the WT protein potentially disrupting KIF5A-mediated transport, as already proposed for ALS-KIF5A [99, 100]. Additionally, the authors speculated on a potential impairment of $GABA_AR$s, central players in inhibitory neurotransmission whose trafficking depends on the interaction between GABARAP and the 73-amino acid sequence unique to the KIF5A tail among KIF5s. Therefore, according to Duis and colleagues [107], altered $GABA_AR$ delivery to synapses due to NEIMY-KIF5A LOF may account for the myoclonic seizures affecting patients. This is consistent with the epileptic phenotype characterising neuron-specific *Kif5a* KO mice [11].

We recently demonstrated that NEIMY-KIF5A mutants share most of their aberrant features with ALS-KIF5A, consistently with the high similarity of their elongated tails. Indeed, both ALS- and NEIMY-KIF5A are deprived of autoinhibition and are aggregation-prone proteins that sequester WT KIF5A, and their aggregates do not co-distribute with mitochondria. At the same time, we also found that NEIMY-KIF5A displays higher aggregation propensity and sequestration capacity compared to ALS-KIF5A. Moreover, NEIMY-KIF5A aggregates exhibit poor dynamicity with respect to ALS-KIF5A. These characteristics implicate a solid-like behaviour that could explain the higher severity of the NEIMY phenotype with compared to ALS [83].

Conclusions

Our literature review, combined with our recently published results [83], outlines the central importance of KIF5A in neuronal physiology. Indeed, while *KIF5B* and *KIF5C* are not found mutated in neurological diseases, the *KIF5A* gene is targeted by a large number of disease-causing mutations. Since many of KIF5A roles in axonal transport are shared with other kinesins, the trafficking processes that are unique to KIF5A must be essential for neuronal function.

Although *KIF5A* variants clustering within distinct protein domains are often linked to different diseases, several molecular defects seem to be shared between *KIF5A*-linked conditions (Fig. 4). For example, most *KIF5A* mutations associated with SPG10 or CMT are generally considered to cause a loss of KIF5A transport competence. However, in at least two cases, the mutations causing SPG10 and CMT are truncating mutations (p.Q764* and p.R864*) that eliminate the tail domain, determining loss of autoinhibition and acting in a dominant-negative manner by sequestering WT KIF5A. Comparably, ALS-linked *KIF5A* mutations are mainly

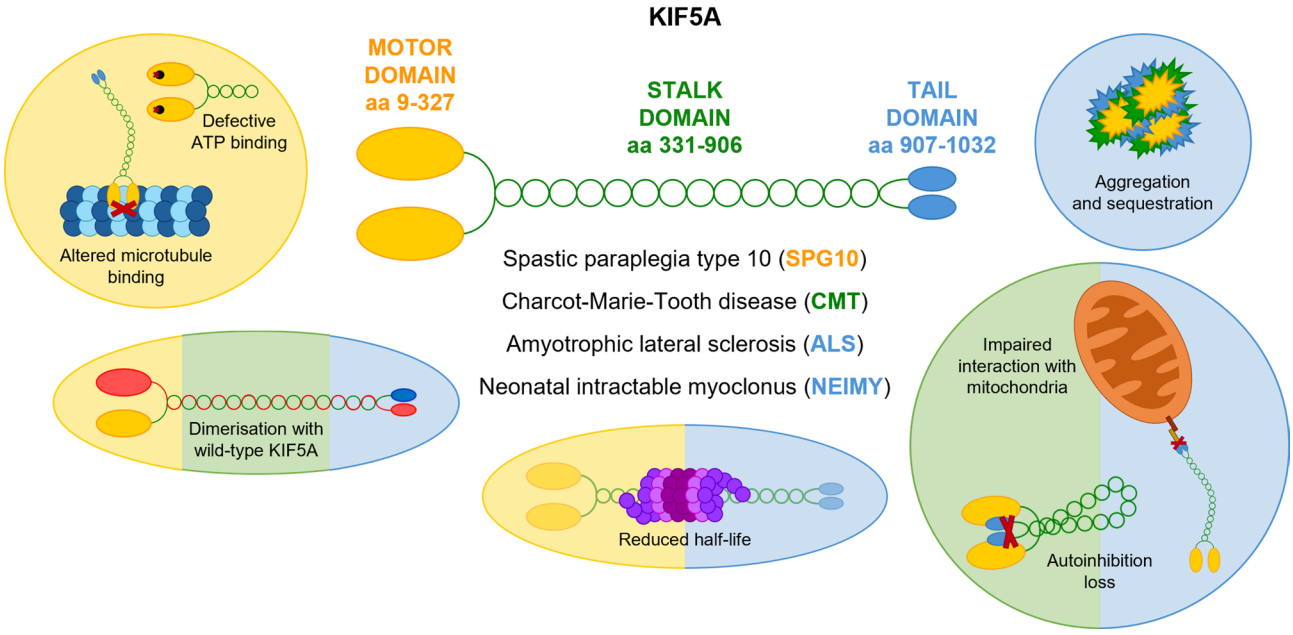

Fig. 4 Schematic representation of the main molecular mechanisms underpinning KIF5A-linked neurodegenerative and neurodevelopmental diseases depending on the affected protein domain. Adapted from Cozzi M, Magri S et al. Altered molecular and cellular mechanisms in KIF5A-associated neurodegenerative or neurodevelopmental disorders. *Cell Death Dis* 2024; 15: 692 [83].

expected to produce a toxic GOF due to protein aggregation and enhanced kinesin motility. Nevertheless, ALS-KIF5A also exhibits LOF features, such as an enhanced protein turnover and the likely inability to interact with KIF5A cargoes, at least in the aggregated state. In a similar way, NEIMY-related *KIF5A* mutations are predicted to cause a loss of transport competence, but the aberrant KIF5A tail they generate also promotes the formation of neurotoxic aggregates as for ALS-KIF5A. Overall, GOF *KIF5A* mutations causing protein aggregation result in more severe phenotypes compared to LOF mutations. Indeed, both upper and lower motor neurons are involved in the case of *KIF5A*-linked ALS and excitatory and/or inhibitory neurons may be involved, too, in the case of NEIMY. Regarding LOF *KIF5A* mutations, haploinsufficiency is probably not a cause since it is not pathogenic in animal models. Additionally, other kinesins transporting the same cargoes as KIF5A may partially compensate its LOF, making the associated phenotypes less aggressive. The likely mechanism of most LOF *KIF5A* mutations is a dominant-negative effect whereby WT-mutant KIF5A heterodimers assemble but are not active. In other cases, the mutations may selectively impair only one KIF5A function (e.g. ATP or microtubule binding) in both heterodimers and mutant KIF5A homodimers, thus leading to cargo sequestration to transport-incompetent motors.

The partial overlap between pathogenic mechanisms related to distinct *KIF5A*-linked disorders raises the question of why some patients develop one phenotype and not the other when *KIF5A* is mutated. For the *KIF5A* mutations associated with both SPG10 and axonal CMT, the genetic backgrounds of differentially diagnosed patients are likely playing a role in the manifestation of distinct diseases. Nevertheless, different neuronal subpopulations are affected by the distinct *KIF5A*-linked neurological disorders. This suggests that each neuronal subtype is differentially susceptible to KIF5A LOF and GOF for reasons that are still to be explored. Thus, further investigation is needed to better understand the factors predisposing affected subjects to develop one or the other *KIF5A*-related phenotypes, as well as to identify the most relevant molecular defects to target with pharmacological intervention in each neuronal subtype.

Abbreviations

ALS	Amyotrophic lateral sclerosis
ALS/FTD	Amyotrophic lateral sclerosis/frontotemporal dementia
AMPAR	α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor
CMT	Charcot-Marie-Tooth
DPYSL2/CRMP2	Dihydropyrimidinase like 2
fALS	Familial ALS
GABA	γ-aminobutyric acid
$GABA_AR$	Gaba type A receptor
GABARAP	$GABA_AR$-associated protein
GABARAPL	$GABA_AR$-associated protein-like
GAP43	Growth associated protein 43
GluR2	Glutamate receptor 2
GOF	Gain of function
GRIP1	Glutamate receptor-interacting protein 1
GSK3β	Glycogen synthase kinase 3β
HAP1	Huntingtin-associated protein 1
hESC	Human embryonic stem cell
IAK	Isoleucine-alanine-lysine

iPSC	Induced pluripotent stem cell
KD	Knock-down
Khc	Kinesin heavy chain
KIF	Kinesin family member
KLC	Kinesin light chain
KO	Knock-out
LOF	Loss of function
LRP8/APOER2	LDL receptor related protein 8
MAPK	Mitogen-activated protein kinase
NEIMY	Neonatal intractable myoclonus
NF	Neurofilament
NMDA	N-methyl-D-aspartate
NMJ	Neuromuscular junction
RAB	Ras oncogene family member
RAN	RAN, member RAS oncogene
RANBP2	RAN binding protein 2
RHOT/Miro	Ras homology family member T
sALS	Sporadic ALS
SFPQ	Splicing factor proline/glutamine-rich
SNAP	Synaptosome-associated protein
SNARE	SNAP receptor
SOD1	Superoxide dismutase 1
SPG	Spastic paraplegia
SQSTM1/p62	Sequestosome 1/p62
TDP-43	TAR DNA-binding protein 43
TRAK/Milton	Trafficking kinesin protein
WT	Wild type

Supplementary Information

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Supplementary Material 1

Author contributions

MCo and AP contributed to conception; MCo drafted the manuscript and prepared the figures; AP, RC, FT supervised the manuscript; MCo, BT, VF, MCh, performed literature research; PP, LC, RM, MB, AM, CM, MP, MG, PR, VC, CG, and SM critically revised the manuscript. All authors read and gave their final approval to the present version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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