Shared behaviours of KIF5A frameshift mutants in neurodevelopment and neurodegeneration

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KIF5A is a neuron-specific kinesin driving anterograde axonal transport. While missense mutations in KIF5A motor and stalk domains cause spastic paraplegia and Charcot-Marie-Tooth disease, translational frameshifts in KIF5A tail domain are linked to amyotrophic lateral sclerosis (ALS) and to a neurodevelopmental condition named neonatal intractable myoclonus (NEIMY). Despite the evident phenotypic differences between ALS and NEIMY, the underpinning KIF5A-related mutations share abnormal reading frame and stop codon, producing elongated KIF5A variants with 40 mutated residues in common. Based on these premises, we compared the biochemical behaviour of two representative ALS-KIF5A (p.N999VfsX39) and NEIMY-KIF5A (p.C975VfsX73) mutants to identify unique and shared features between them.
Bioinformatic analysis of ALS- and NEIMY-KIF5A C-terminal sequences revealed that their common aberrant tail is composed of poorly soluble amino acids, differently from wild-type (WT) KIF5A. Of note, an additional low-solubility sequence was present in the NEIMY-KIF5A mutant but absent in the ALS-KIF5A one. Consistently, upon overexpression both mutants displayed low detergent solubility, but NEIMY-KIF5A accumulated into larger inclusions compared to ALS-KIF5A. The increased tendency to form condensates of the NEIMY-KIF5A mutant was also accompanied by higher WT KIF5A sequestration with respect to the ALS-KIF5A mutant, hinting at a stronger dominant-negative effect. Moreover, both ALS- and NEIMY-KIF5A mutants puncta co-localised with the ubiquitin-binding protein SQSTM1/p62, but the autophagy receptor was only found at the rim of NEIMY-KIF5A inclusions. Interestingly, both ALS- and NEIMY-KIF5A mutants accumulated upon proteasomal blockage, while no autophagy involvement was found in mutant KIF5A degradation. Finally, both mutants poorly co-localised with mitochondria, a well-established KIF5A cargo.
Together, our observations indicate that most biochemical behaviours characterising ALS-KIF5A appear exacerbated for NEIMY-KIF5A, consistently with a more severe phenotype, and that a combination of gain- and loss-of-function mechanisms may be at the basis of both KIF5A-linked conditions.
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