Expanding the natural history of *KIF1A* associated neurological disorders (KAND)

Lia Boyle[1], Wendy K. Chung[1,2]

1) Columbia University College of Physicians and Surgeons, New York, NY, 2) Department of Pediatrics, Columbia University Medical Center, New York, NY

Introduction

- *KIF1A* encodes for a kinesin responsible for anterograde axonal transport of synaptic-vesicle precursors and neurotransmitters.
- Pathogenic variants in *KIF1A* have been associated with distinct disorders including the peripheral nervous system disorder hereditary sensory neuropathy IIC (HSN2C), the central nervous system upper motor neuron disorder hereditary spastic paraplegia-30 (SPG30), as well as a complex syndrome with a constellation of symptoms including axonal hypotonia, peripheral spasticity, intellectual disability, and variable cerebellar and cerebral atrophy (MRD9).
- Although pathogenic variants in *KIF1A* were initially assigned to each of these distinct diagnostic categories based on phenotype and mode of inheritance, as we expand our understanding of the natural history of these disorders, these discrete disorders are really a spectrum of clinical severity across *KIF1A* Associated Neurological Disorders.

Methods

- Cohort includes 22 individuals, 1 of whom (an individual with the p.E253K variant) died prior to study enrollment
- 14 males, 8 females, 5 months - 21 years old (mean=8.1 years, median=5.6 years)
- 20/22 individuals are heterozygous with one pathogenic variant. 17/20 variants are confirmed de novo, though parental testing is not available for 3/20.
- 2 /22 individuals are compound heterozygotes with one variant inside the motor domain and one outside.
- Data collected includes caregiver reported medical history (***Table 1***), copies of clinical genetic test reports (***Figure 1***), and Vineland Adaptive Behavior Scales-II (VABS-II) (***Figure 2***)

Results

Figure 1: Vineland Adaptive Behavior Scales domains and subdomains

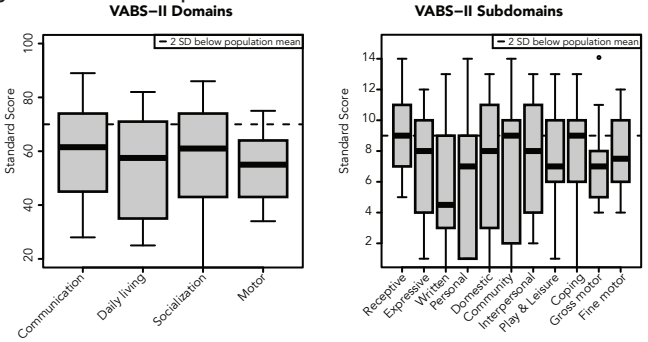
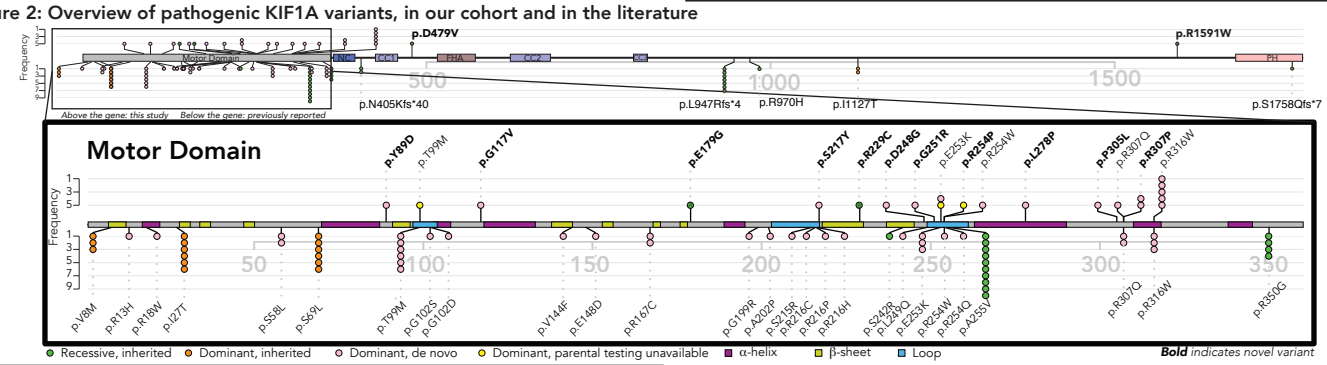


Table 1: Phenotypic manifesations of KAND

	Dominant N=20	Recessive N=2
Neurological Issues	100% (20/20)	100% (2/2)
Hypotonia	80% (16/20)	100% (2/2)
Hypertonia	70% (14/20)	50% (1/2)
Microcephally	40% (8/20)	0% (0/2)
Abnormal MRI	90% (18/20)	50% (1/2)
Developmental delay	100% (20/20)	100% (2/2)
Seizures	45% (9/20)	100% (2/2)
Grand mal	20% (4/20)	50% (1/2)
Petit mal	25% (5/20)	50% (1/2)
Ophthalmological Issues	85% (17/20)	100% (2/2)
Cataracts	5% (1/20)	50% (1/2)
Cortical visual impairment	20% (4/20)	0% (0/2)
Optic nerve abnormalities *(hypoplasia or atrophy)*	40% (8/20)	0% (0/2)
Ptosis	5% (1/20)	0% (0/2)
Strabismus	15% (3/20)	50% (1/2)
GERD	50% (10/20)	100% (2/2)
Eczema	50% (10/20)	100% (2/2)
Genital abnormalities *(Only seen in males. Includes micropenis, microorchidism, and cryptorchidism)*	15% M: 25% (3/12) F: 0% (0/8)	0% M: 5% (0/2) F: 0% (0/0)

Figure 2: Overview of pathogenic KIF1A variants, in our cohort and in the literature



Conclusions

- 9 individuals have novel de novo variants in the *KIF1A* motor domain (p.Y89D, p.G117V, p.S217Y, p.D248G, p.G251R, p.L278P, p.P305L, p.R307P)
- New features not previously observed in KAND include a high prevalence of gastrointestinal reflux (55%) and multiple males with genital abnormalities including micropenis, microorchidism, and cryptorchidism.
- Patients with the recurrent p.E253K variant have severe neonatal hypotonia and 3 of the known 5 individuals died before 4 years of age

References

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- Tomaselli PJ, Rossor AM, Horga A, et al. A de novo dominant mutation in KIF1A associated with axonal neuropathy, spasticity and autism spectrum disorder. *J Peripher Nerv Syst*. 2017;95:590. doi:10.1111/jns.12235.

Acknowledgements

We extend our gratitude to the families and their children with KAND who participated in this study, and to the family organization KIF1A.org for partially financing the study.

Contact: Lia Boyle: lb2905@cumc.columbia.edu Wendy K Chung: wkc15@cumc.columbia.edu