Ovid® THERAPEUTICS

BOLDMEDICINE

(NASDAQ: OVID)

Greetings to the KAND Community

AMIT RAKHIT, MD, MBA

PRESIDENT AND CHIEF MEDICAL OFFICER

Working Hand-in-Hand with the KAND Community

Together we are strong: The KAND community makes our work possible
You are why we come to work every day

2017

2019

We Understand What is Truly Meaningful

PATIENTS AND FAMILIES

- Understand what matters most to KAND families
- Integrate and include patients & caregivers in development process from day one

SCIENTIFIC COMMUNITY

- Raise awareness in the scientific community and collaborate with researchers

RARE DISEASE COMMUNITY

- Create therapies that have the potential to transform the lives of patients and families

ADVOCACY ORGANIZATIONS

- Work together to address the urgent need for treatment of severe neurological conditions that have limited or no therapeutic options

Together With Our Patient Communities We Accelerate R&D

Ovid Therapeutics is developing **medicines** based on our **understanding of key biological pathways** and their **central role** in rare neurological conditions

We develop medicines using **clinically relevant criteria** ***related*** to the **underlying disease pathophysiology** to capture potential **benefits** as they relate to families and patients in the **real-world**

We do this with a **focused effort** on the significant **unmet therapeutic need** in a **sentinel indication**

With **demonstrated success** we **apply** ***science-driven, patient-focused, family-focused*** expertise to other conditions where we hope to make a **unique difference** for **people living with serious conditions and their families and loved ones**

Thank you

from all of us at Ovid Therapeutics

for allowing us to be a part of your journey

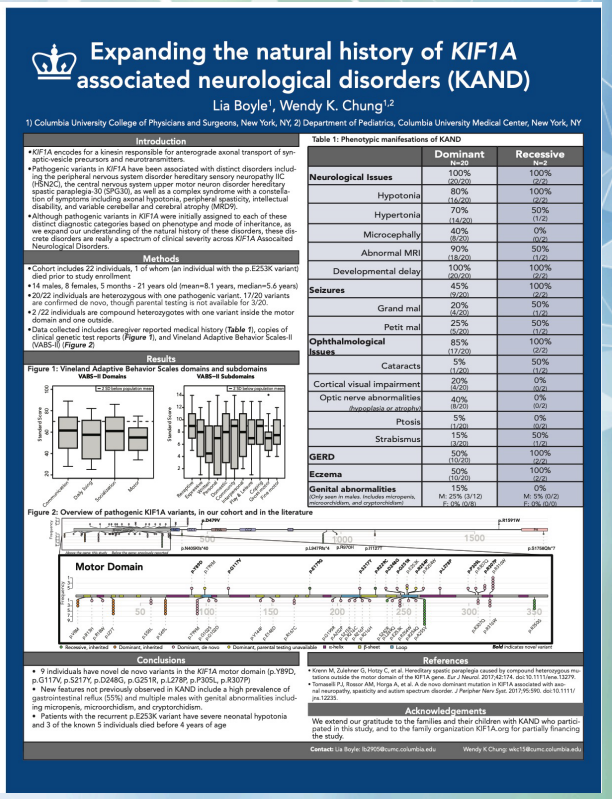
OV815: KIF1A (KAND) Preclinical Gene Modulation

KIF1A ASSOCIATED NEUROLOGICAL DISORDER (KAND)

KIF1A is primarily an autosomal dominant, gain of function disorder with mutations impacting the transport of synaptic vesicle precursors to the synapse

Natural History Data from Chung Lab – Columbia University

- Neurological concerns
  - Hypotonia: 85%
  - Hypertonia/spasticity: 75%
  - Seizures: 44% (likely underreported due to multiple seizure types)
  - Abnormal MRIs (e.g. cerebellar atrophy): 58%
- Eye concerns
  - Vision or eye conditions: 85%
  - Optic nerve atrophy: 40%
- Intellectual disability
- Peripheral neuropathy
- Autism, obsessive compulsive behavior and anxiety
- Endocrine, kidney and urogenital issues reported but less common
- Patients without genetic test have been diagnosed with Cerebral Palsy, Charcot Marie Tooth (CMT), RETT



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

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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 (MRO9).
- 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 manifestations 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)
Microcephaly	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% (6/20)	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: 9% (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.L278F, 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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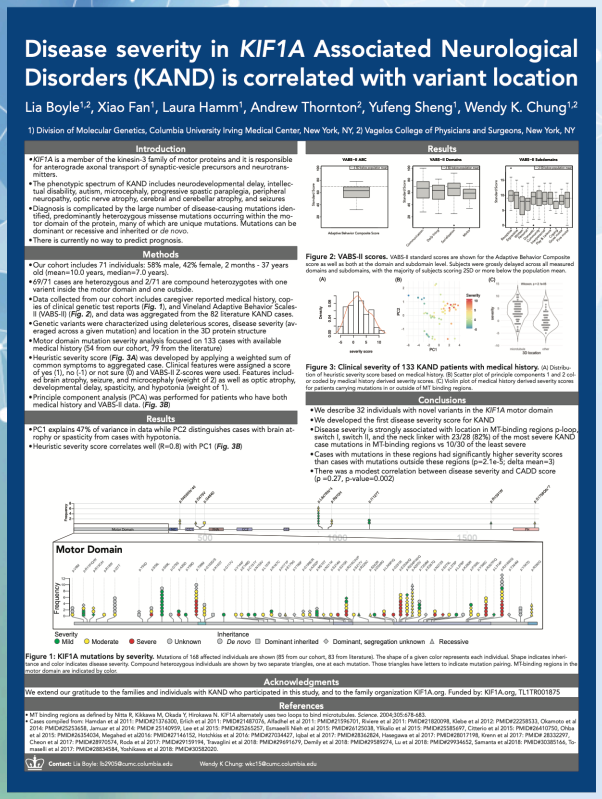

Disease severity in *KIF1A* Associated Neurological Disorders (KAND) is correlated with variant location

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Introduction

- *KIF1A* is a member of the kinesin-3 family of motor proteins and it is responsible for anterograde axonal transport of synaptic-vesicle precursors and neurotransmitters.
- The phenotypic spectrum of KAND includes neurodevelopmental delay, intellectual disability, autism, microcephaly, progressive spastic paraplegia, peripheral neuropathy, optic nerve atrophy, cerebral and cerebellar atrophy, and seizures
- Diagnosis is complicated by the large number of disease-causing mutations identified, predominantly heterozygous missense mutations occurring within the motor domain of the protein, many of which are unique mutations. Mutations can be dominant or recessive and inherited or de novo.
- There is currently no way to predict prognosis.

Methods

- Our cohort includes 71 individuals: 58% male, 42% female, 2 months - 37 years old (mean=10.0 years, median=7.0 years).
- 69/71 cases are heterozygous and 2/71 are compound heterozygotes with one variant inside the motor domain and one outside.
- Data collected from our cohort includes caregiver reported medical history, copies of clinical genetic test reports (**Fig. 1**), and Vineland Adaptive Behavior Scales-II (VABS-II) (**Fig. 2**), and data was aggregated from the 82 literature KAND cases.
- Genetic variants were characterized using deleterious scores, disease severity (averaged across a given mutation) and location in the 3D protein structure
- Motor domain mutation severity analysis focused on 133 cases with available medical history (54 from our cohort, 79 from the literature)
- Heuristic severity score (**Fig. 3A**) was developed by applying a weighted sum of common symptoms to aggregated case. Clinical features were assigned a score of yes (1), no (-1) or not sure (0) and VABS-II Z scores were used. Features included brain atrophy, seizure, and microcephaly (weight of 2) as well as optic atrophy, developmental delay, spasticity, and hypotonia (weight of 1).
- Principle component analysis (PCA) was performed for patients who have both medical history and VABS-II data. (**Fig. 3B**)

Results

- PC1 explains 47% of variance in data while PC2 distinguishes cases with brain atrophy or spasticity from cases with hypotonia.
- Heuristic severity score correlates well (R=0.8) with PC1 (**Fig. 3B**)

Results

Figure 2: VABS-II scores.

Figure 3: Clinical severity of 133 KAND patients with medical history.

Conclusions

- We describe 32 individuals with novel variants in the *KIF1A* motor domain
- We developed the first disease severity score for KAND
- Disease severity is strongly associated with location in MT-binding regions p-loop, switch I, switch II, and the neck linker with 23/28 (82%) of the most severe KAND case mutations in MT-binding regions vs 10/30 of the least severe
- Cases with mutations in these regions had significantly higher severity scores than cases with mutations outside these regions (p=2.1e-5; delta mean=3)
- There was a modest correlation between disease severity and CADD score (p =0.27, p-value=0.002)

Figure 1: KIF1A mutations by severity.

Acknowledgments

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References

- MT binding regions as defined by Nitta R, Kikkawa M, Okada Y, Hirokawa N. KIF1A alternately uses two loops to bind microtubules. *Science.* 2004;305:678-683.
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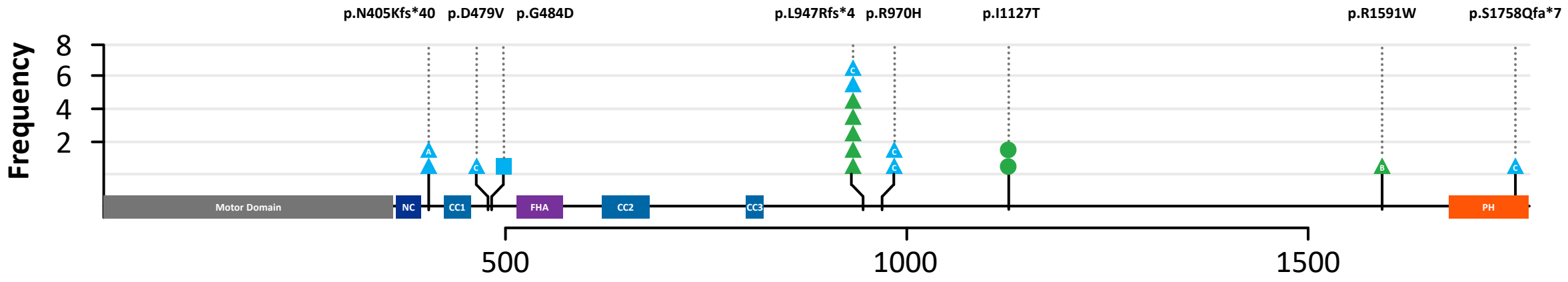
KIF1A-Associated Neurological Disorder (KAND)

- KIF1A (Kinesin-3 Family Member)
  - KIF1A is a unique monomeric microtubule motor; neuron specific
  - Responsible for anterograde transport of synaptic vesicles, organelles and neurotransmitters
  - Intrinsic weak binding of KIF1A to GTP-tubulin induces motor detachment at pre-synapses altering synaptic strength
  - Majority of mutations occur within the motor domain

Severity: Mild Moderate Severe Unknown **Inheritance:** De novo Dominant inherited Dominant, segregation unknown Recessive



KAND Therapeutic Approaches

- Knockdown defective allele
- Disable mutant protein
- Replace defective gene
- Expand understanding of global cellular pathways affected by individual KIF1A variants
  - Alternative approach targeting other signaling/transport/trophic support pathways.
  - Use patient or isogenic derived iPSCs for characterization
  - Some similarities in KIF1A variant structure with other kinesin family members and kinesin family interacting proteins (MAPs, Tau, etc)

Approach to KAND Therapies

KIF1A Mutant **Neutralization**

KIF Mutant Neutralization → Aptamer Protein Targeting → Library Screening

↓

Dimerization Destabilization/Disruption

↓

Functional Testing (Biochemical) | In vitro Validation | Lead Identification

KIF1A Mutant **Knockdown**

KIF1 Mutant Knockdown → RNAi Gene Targeting → Library Screening

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Reduction of Mutant Expression

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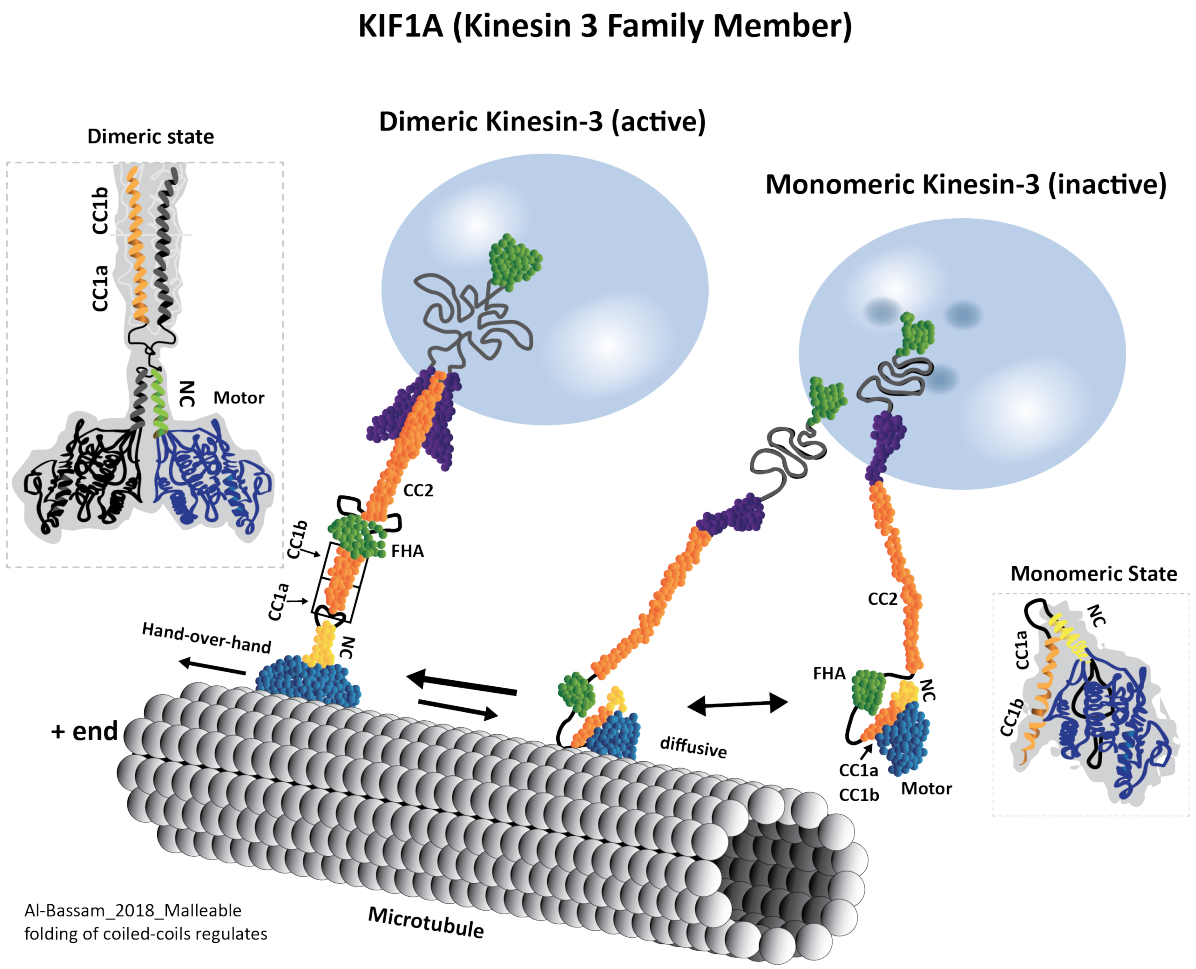
In vitro Validation | Lead Identification | Viral Delivery Development



Al-Bassam_2018_Malleable folding of coiled-coils regulates

Ovid THERAPEUTICS BOLDMEDICINE

Thank you for including us in this fight to change KAND's fate.