What We’ve Learned from the KAND Natural History Study
Speaker: Lia Boyle, Chung Lab, Columbia University
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Visit kif1a.org/2019Conference to watch a recording of this presentation.
What is a natural history study?

• Tracks the course of a disease over time
• Helps identify variables that correlate with disease outcomes in the absence of a specific treatment
• “Pillar of epidemiologic research on rare conditions” – Institute of Medicine*

*Institute of Medicine. 2010. Rare Disease and Orphan Products. Accelerating Research and Development
Why a natural history study?

• Begin with the end in mind!

Slide adapted from Anne Pariser, MD, Center for Drug Evaluation and Research, USFDA
Why a natural history study?

• Begin with the end in mind!
• Foundational for drug development
• “The top reason why rare disease development programs fail at FDA is the lack of natural history information” – Christopher Austin, head of NIH’s National Center for Advancing Translational Sciences*


Slide adapted from Anne Pariser, MD, Center for Drug Evaluation and Research, USFDA
What we knew
First KIF1A patients: 2011

• Single KIF1A case
• Hypotonia, spasticity, and intellectual disability
• Spontaneous p.T99M mutation
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- 3 people from one family
- Difficulty walking and leg spasticity, no cognitive issues
- Recessive p.A255V mutation
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**MRD9**

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**SPG30**

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KIF1A, an Axonal Transporter of Synaptic Vesicles, Is Mutated in Hereditary Sensory and Autonomic Neuropathy Type 2

Jean-Baptiste Rivière,1,2,3,4 Srinivasa Ramalingam,2,3,4,5 Valérie Lavastre,1,2,3 Massoud Shekarabi,1,2,3 Sébastien Hébert,1,2,3 Julie Lafontaine,1,2,3 Myriam Sour,1,2,3 Nancy Menner,1,2,3 Daniel Rochefort,1,2,3 Pascale Hicke,1,2,3 Rebecca Gaudet,1,2,3 Anne-Marie Mes-Masson,4 Jonathan Baets,4,5 Henry Houlden,7 Bernard Bras,1,2,3 Garrath A. Nicholson,9,10 Hilde Van Esch,1,11 Shabtai Natoli,11 Peter De Jonghe,1,2,3 Mary M. Reilly,3 Vincent Timmerman,3 Patrick A. D’Hooge,1,2,3 and Guy A. Rouleau1,2,3,4,5

1Whitehead Institute for Biomedical Research, Cambridge, Massachusetts 02142, USA; 2Montreal and Jacques Raich Department of Genomic Research, Department of Genomic and Metabolic Diseases, Hadassah, Hebrew University Medical Center, 91120 Jerusalem, Israel; 3Weiner School of Biological Sciences, Harvard Medical School, Imperial College, London, New York 11224, USA
First KIF1A patients: 2011

MRD9

Excess of De Novo Deleterious Mutations in Genes Associated with Glutamatergic Systems in Nonsyndromic Intellectual Disability

• Single KIF1A case
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SPG30

Exome sequencing and disease-network analysis of a single family implicates a mutation in KIF1A in hereditary spastic paraparesis

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HSN IIC

KIF1A, an Axonal Transporter of Synaptic Vesicles, Is Mutated in Hereditary Sensory and Autonomic Neuropathy Type 2

• 8 people from 4 families
• Sense perception issues and problems regulating autonomic system
• Recessive truncating mutations
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KIF1A Associated Neurological Disorder (KAND)

• Can result from changes in one copy of a person’s KIF1A gene (*dominant*) or both copies (*recessive*)
• Changes can be inherited or occur spontaneously (*de novo*)
• Some spontaneous changes occur again and again in many different people
• Many individuals with a spontaneous change may be the only person we know of (*so far!*) with that particular change
Gene layout

**Functional domains**
- Neck coil
- Coiled coil
- Forkhead associated
- Pleckstrin homology

**Microtubule binding regions**
- P-loop
- Switch I
- Switch II
- Neck linker
KIF1A Family Meeting 2017

• More than 30 people (10+ in person, 20+ online)
KAND then
Yellow: inherited, dominant
Green: inherited, recessive
What we’ve learned
Methods: study enrollment

• Potential participant reaches out to us
• Initial information collected to determine eligibility
• Variants reviewed by researchers, eligible individuals invited to participate
• Study described in detail, consent obtained in person or online
Methods: data collection

• Initial medical history interview via phone/skype
• Medical records collected (including genetic test, MRI and EEG data)
• Parent or caregiver completes Vineland Adaptive Behavior Scales (English/Spanish speakers only)
  • Second edition previously completed via call
  • Third edition now completed online
KAND across the world
22 countries
23 states (and DC!)

KAND across the world
Study enrollment

- Express interest: n=148
  - Lost to follow up: n=11
    - Gathering test: n=4
  - Variants known: n=133
    - Likely not KIF1A: n=19
  - Predicted pathogenic: n=114
    - Consented: n=89
      - Have genetic test: n=83
        - Medical history interview: 81
          - Complete: 71
          - Partial: 10
          - Either Vineland: 76
            - VABS-II: 39
            - VABS-III: 67
      - Need genetic test: n=6
        - Medical history interview: 5
          - Either Vineland:
            - VABS-II: 1
            - VABS-III: 4
    - Not consented: n=25
      - Language barriers: n=10
        - In process: n=10
        - Lost to follow up: n=5
Study enrollment

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Mutation type breakdown

- Total: n=89
  - Splicing: n=1
  - SNP: n=88
    - Dominant: n=86
      - No test in hand: n=6
        - De novo: n=56
        - Dominant inherited: n=4
        - Mosaic: n=1
        - Unknown: n=19
    - Recessive: n=2
Participant demographics

- Female: 46% (38/83)
- Male: 56% (45/83)
- Average age: 10 years old (5 months – 38 years)
Neurological concerns

• Hypotonia: 85% (64/75)
• Hypertonia/spasticity: 75% (62/78)

• Smaller than expected head size (microcephaly): 21% (16/75)
• Larger than expected head size (macrocephaly): 3% (2/76)

• Previous diagnosis of cerebral palsy: 24% (18/74)
Seizures and epilepsy: an overview

- Seizures: 44% (35/80)
- No seizures: 56% (45/80)

- Out of those *without* seizures, a little more than half have had an EEG (26/45)
  - No seizures, normal EEG: 73% (19/26)
  - No seizures, abnormal EEG: 35% (9/26)
Average age at first seizure: 5 years (median: 2.5 years)
Most people with seizures have had more than 4 total (30/35)
Seizures and epilepsy: details

• Seizure types: (16/35 have multiple types)
  • Petit mal/absence: 63% (22/35)
  • Grand mal: 34% (12/35)
  • Atonic drop seizures: 20% (7/35)
  • Infantile spasm: 9% (3/35)
  • Focal seizures: 9% (3/35)
  • Complex partial: 3% (1/35)

• Treatment refractory: 14% (5/35)
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NEXT STEP: Detailed survey on seizures will be emailed this fall!
Neuroimaging: overview

- Most people have had some neuroimaging: 97% (74/76)
- Normal MRIs: 41% (30/74) (average age 4.3y)
- Abnormal MRIs: 58% (43/74) (average age 3.8y)
  - Previous normal MRI: 8% (6/74)
  - Abnormal MRIs only: 50% (37/74)
Neuroimaging details (changes over time)

- Cerebellar atrophy most common: 35% (26/74)
- Abnormalities of the corpus callosum: 11% (8/74)
- Cerebral atrophy: 5% (4/74)
- Other reported abnormalities: 32% (24/74)
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• Next step: we need your original images so our team can directly review!
Eye findings

- Issues with vision, eyes or eyesight: 88% (67/76)
Kidney

- Renal issues: 16% (12/74)
  - Urinary reflux: 3% (2/74)
  - Other: 15% (11/74) (e.g., absent kidney, swelling of part of the kidney or the whole kidney, bladder obstruction, calcification of the kidney, excreting protein in the urine, structural abnormalities of bladder and kidney, urinary urgency)
Urogenital findings: 17% (13/75)
  • In females: 6% (2/33)
    • Slight, clinically irrelevant, differences in external female genitalia
  • In males: 26% (11/43)
    • 8/43: micropenis, small scrotum
    • 2/43: undescended testicles
    • 1/43: hypospadias
Endocrine

- Endocrine issues: 30% (23/77)
  - Short stature: 16% (12/77)
  - Growth hormone deficiency: 5% (4/77)
    - Complete growth hormone deficiency: 3/77*
    (*Previously reported in literature)
    - Mild growth hormone deficiency: 1/77
Additional findings

- Difficulty swallowing, requiring gastrostomy tube: 11% (8/76)
- Eczema: 26% (20/76) (an additional 10/76 reported dry skin)
- Reflux (heart burn): 38% (29/76)
Additional findings

• Increased prevalence of autism, obsessive compulsive behavior and anxiety
• Increased pain tolerance
• Small, cold hands and feet
• Difficulty regulating temperature
• Sleep issues
Vineland adaptive behavior scores: VABS-II

N=39
Vineland adaptive behavior scores: VABS-III

N=67
What we don’t see

• No problems with hearing
• No congenital heart disease or problems with the heart
• No autoimmune conditions
• No increased risk of cancer
Summary

- Most common symptoms are issues with nerves (increased and decreased muscle tone and spasticity)
- Seizures are common, with the most frequent seizure types being absence (63%) and grand mal (34%)
- Abnormal EEGs can be seen without clinical seizures, some people with seizures have normal EEG
- Among vision problems, optic nerve atrophy most common
- Growth hormone deficiency is an uncommon finding
Next steps: what we need from you

- Rare Epilepsy Survey: enrolled participants will receive an email with a survey link
- Original MRI images, EEG tracings submitted to us
- Annual follow up with updates, submitted online
## Acknowledgments

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Our collaborators

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From KIF1A.ORG:
Learn more about the KAND Natural History Study at
www.kif1a.org/research/natural-history-study/