KIF1A Family Meeting

August 13, 2022
The Goal of this Research

- To support development of treatments for *KIF1A*
- To describe changes in development and health issues over time
- Develop clinical care guidelines
- To understand differences in manifestations according to the variant in the *KIF1A* gene
KIF1A associated neurological disorder (KAND)

Spectrum of conditions caused by pathogenic variants in the gene KIF1A

*De novo*, missense variants

Ranges from severe congenital disease to adult-onset mild progressive spastic paraplegia

>100 causative variants in ~300 individuals worldwide
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
- Help us learn from each other and develop best practices
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*

KIF1A Natural History Study

Step 1
- Contact Alexa (ag4216@columbia.edu)
  and Sean (sc5009@columbia.edu)

Step 2
- Provide your clinical lab report

Step 3
- Schedule a call with the Genetic Counselor

Ongoing
- Complete the surveys online
KIF1A Family Meeting 2017
KIF1A protein
Molecular motor protein in the nervous system
Transports neuronal cargo in axons & dendrites along microtubules
KIF1A Variants

Microtubule binding regions
- P-loop
- Switch I
- Switch II
- Neck linker

COLUMBIA UNIVERSITY IRVING MEDICAL CENTER
Study eligibility is based upon KIF1A genetics

- Genetic test report is reviewed for eligibility
- Consent obtained online
Methods: data collection

• Initial medical history interview via phone/online
• 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!)
Participant demographics

- Female: 46% (66/142)
- Male: 54% (76/142)
- Average age: ~13 years (range: 1.5 – 59)
KAND: Clinical Snapshot of Symptoms/Features

**Neurological & Behavior**
- Developmental delay/intellectual disability: 92%
  - Seizures: 37%
  - Abnormal MRI: 56%
  - Cerebellar atrophy: 44%

**Stomach & Digestion**
- Reflux: 34%
- Diarrhea: 17%
- Constipation: 35%

**Muscles & Bones**
- Hypotonia: 83%
- Hypertonia: 75%
- Scoliosis: 14%

**Vision & Eyesight**
- Overall vision/eye conditions: 83%
  - Optic nerve atrophy: 43%
  - Cortical visual impairment: 16%
  - Strabismus: 23%

**Urinary & Reproductive**
- Irregularity in genitalia: 18%
- Kidney problems: 23%
- Short stature: 11%
- Absence of growth hormone: 4%
- Peripheral neuropathy: 27%
Neurological concerns

Hypotonia: 83% (118/142)
Hypertonia/spasticity: 75% (106/142)
Smaller than expected head size (microcephaly): 15% (21/142)
Previous diagnosis of cerebral palsy: 29% (41/142)
Seizures and epilepsy

- 37% report seizures (52/142)
- Average age at first seizure: 5 years (median: 3 years)
Seizure types: (48% [25/52] have multiple types)

- Petit mal/absence: 67% (35/52)
- Grand mal: 40% (21/52)
- Atonic drop seizures: 19% (10/52)
- Infantile spasm: 8% (4/52)
- Focal seizures: 12% (6/52)
- Complex partial: 6% (3/52)

Treatment refractory: 6% (3/52)
Seizure Interventions

• 86/142 regularly take any medication (61%)
• Seizure medications
  • Keppra: 17
  • Valproic acid/Depakote: 8
  • Others: ACTH, Lamictal, clobazam, clonazepam, Trileptal, rescue medications
• No participants report VNS or surgical procedure for seizures
• 5 participants report trying the ketogenic diet, 3 of which discontinued as it was not effective
Other Medications

- Baclofen: 13
- Vyvanse: 4
Neuroimaging

- Most people have had neuroimaging: 94% (133/142)
- Abnormal MRI: 56% (74/133)
- Normal MRI: 41% (55/133)
- Unsure of result: 3% (4/133)
Neuroimaging Abnormalities

- Cerebellar atrophy most common: 44% (59/133)
- Abnormalities of the corpus collosum: 20% (26/133)
- Cerebral abnormality: 15% (20/133)
Eye findings

Issues with vision, eyes or eyesight: 83% (118/142)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
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</thead>
<tbody>
<tr>
<td>Optic Nerve Atrophy</td>
<td>61 (43%)</td>
</tr>
<tr>
<td>Strabismus</td>
<td>33 (23%)</td>
</tr>
<tr>
<td>Cortical vision loss</td>
<td>23 (16%)</td>
</tr>
<tr>
<td>Corrective lenses</td>
<td>54 (38%)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>Depth perception issue</td>
<td>10 (7%)</td>
</tr>
</tbody>
</table>
Kidney

Renal issues: 23% (32/142)

• Urinary reflux, absent kidney, hydronephrosis, bladder obstruction, calcification of the kidney, excreting protein in the urine, structural abnormalities of bladder and kidney, urinary urgency
Urogenital anatomical differences

Urogenital findings: 18% (25/142)

• In females: 9% (6/66)
  - Slight, clinically irrelevant, differences in external female genitalia

• In males: 17% (13/76)
  - 11/76: micropenis, small scrotum
  - 2/76: undescended testicles
  - 2/76: hypospadias
Endocrine

Endocrine issues: 22% (31/142)
- Short stature: 11% (15/142)
- Failure to thrive: 8% (11/142)
- Growth hormone deficiency: 4% (5/142)
- Precocious puberty: 2% (3/142)
Gastrointestinal issues

- Requires gastrostomy tube: 6% (8/142)
- Reflux (heart burn): 34% (48/142)
- Constipation: 35% (50/142)
Additional findings

Increased prevalence of autism, obsessive compulsive behavior and anxiety
Increased pain tolerance
Small, cold hands and feet
Blotchy skin
Difficulty regulating temperature
Sleep issues
## Loss of Function Data

<table>
<thead>
<tr>
<th>Loss of Function Variants</th>
<th>Inheritance</th>
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<tbody>
<tr>
<td>c.798+2_798+5del</td>
<td>De novo</td>
</tr>
<tr>
<td>c.798+1G&gt;T</td>
<td>De novo</td>
</tr>
<tr>
<td>c.4911+1G&gt;A</td>
<td>De novo</td>
</tr>
<tr>
<td>c.2839dupC</td>
<td>Unknown</td>
</tr>
<tr>
<td>c.1038-1G&gt;A</td>
<td>De novo</td>
</tr>
<tr>
<td>Compound heterozygous: c.2494C&gt;T, c.2664del</td>
<td>Mat/Pat</td>
</tr>
<tr>
<td>Deletion of entire coding sequence</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

- 6/7 have no seizures
- Of the 5 who have had brain MRI, 4 were normal
- Reported features: hypotonia, hypertonia, previous cerebral palsy diagnosis, scoliosis
• TP 1 average: 62.6
• TP 2 average: 59.9
What we don’t see

No problems with hearing
No problems with the heart
No autoimmune conditions
Summary

• Most common symptoms are issues with nervous system (increased and decreased muscle tone and spasticity)
• Seizures are common, with the most frequent seizure types being absence and grand mal
• Abnormal EEGs can be seen without clinical seizures, some people with seizures have normal EEG
• Among vision problems, optic nerve atrophy most common
Next steps: what we need from you

• Enroll if you have not enrolled
• Submit your genetic test report
• Fill out your baseline surveys
• Complete annual follow ups online
• Rare Epilepsy Survey: enrolled participants will receive an email with a survey link
• Submit original MRI images, EEG tracings
• Are you willing to keep a seizure diary?
KOALA – The In-Person Natural History Study

• 2-day evaluation at Columbia University Medical Center in NYC
• Eligibility: a genetically confirmed KAND diagnosis
• Evaluations include:
  • Motor evaluation
  • Neuropsychological/neurocognitive
  • Ophthalmologic
  • EEG
  • Neurological exam
  • Photos/videos
  • Blood samples
• You may be eligible for travel reimbursement from kif1a.org
• Contact kif1a_study@cumc.Columbia.edu if you are interested in participating
Acknowledgments

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KAND patients and families!

Ovid Therapeutics