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

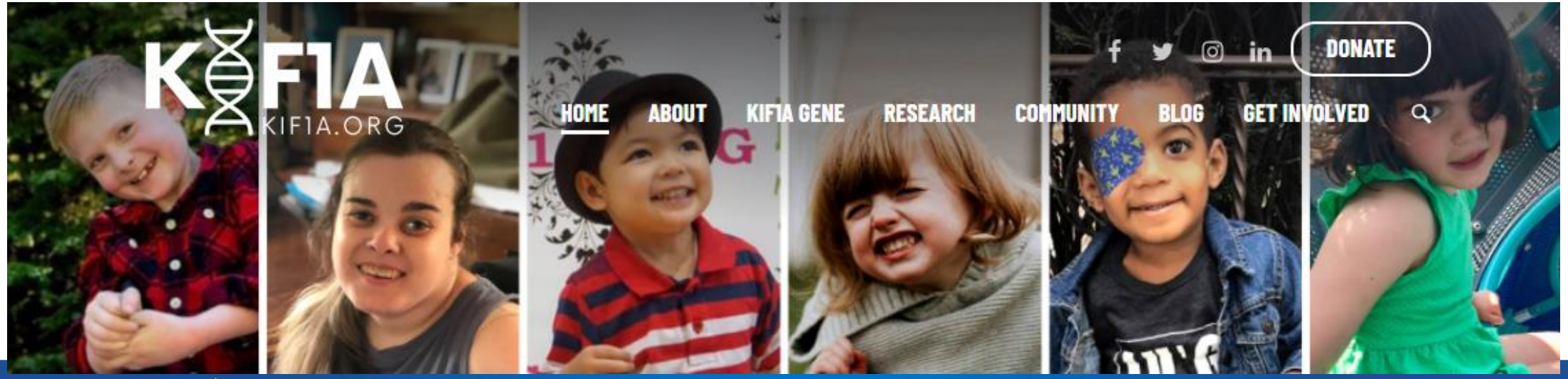
KIF1A associated neurological disorder (KAND)

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



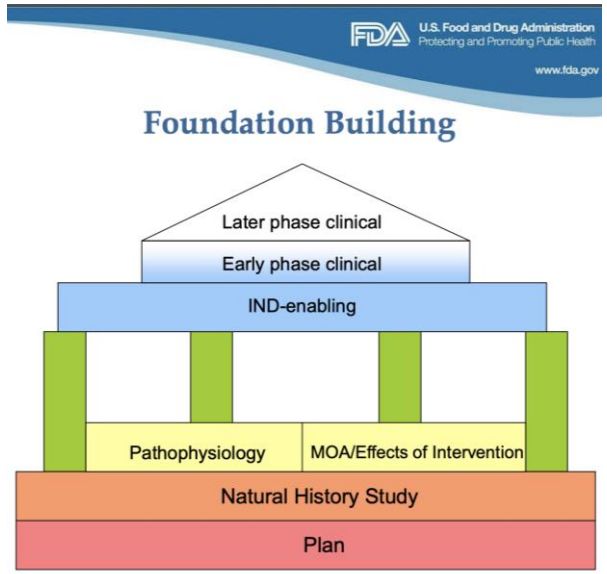
What is a natural history study?

- 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*

Slide adapted from Anne Pariser, MD, Center for Drug Evaluation and Research, USFDA

*Pamela Gavin. Expert Opinion on Orphan Drugs (2015) 3(8):855-857

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

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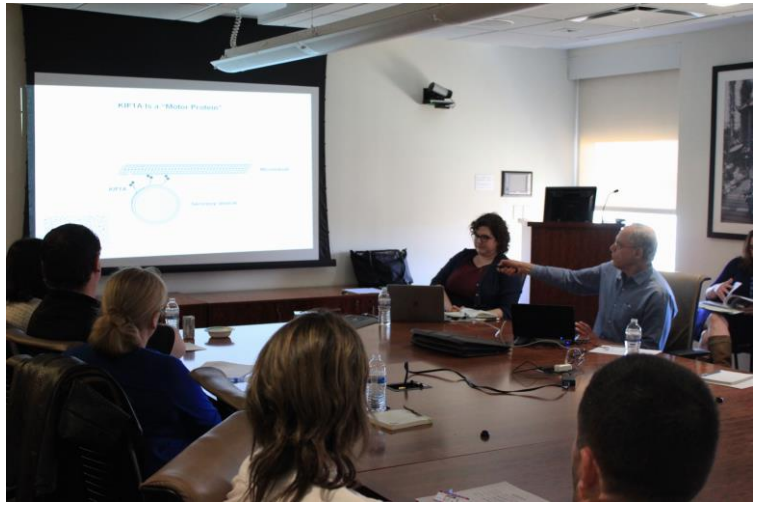
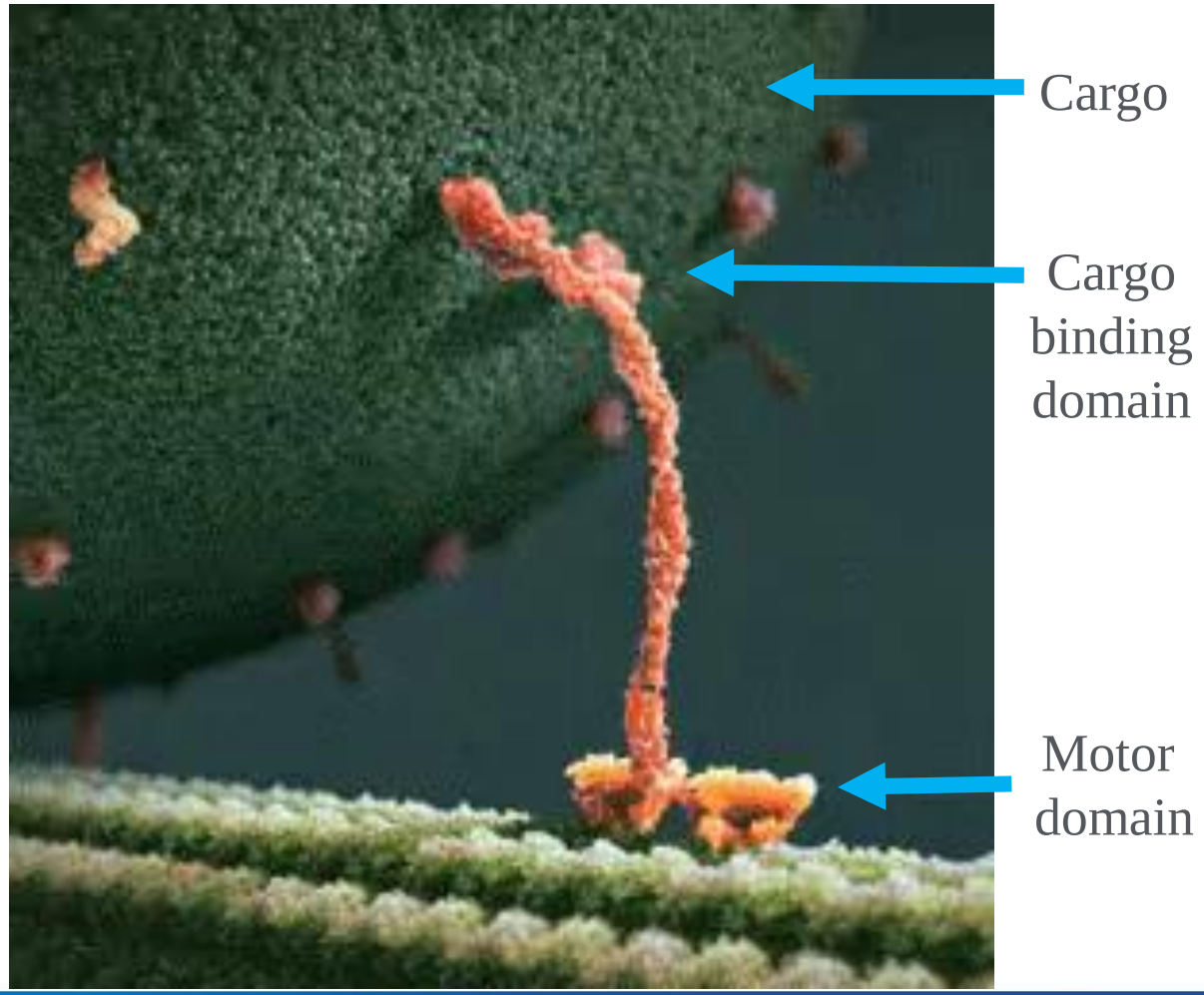


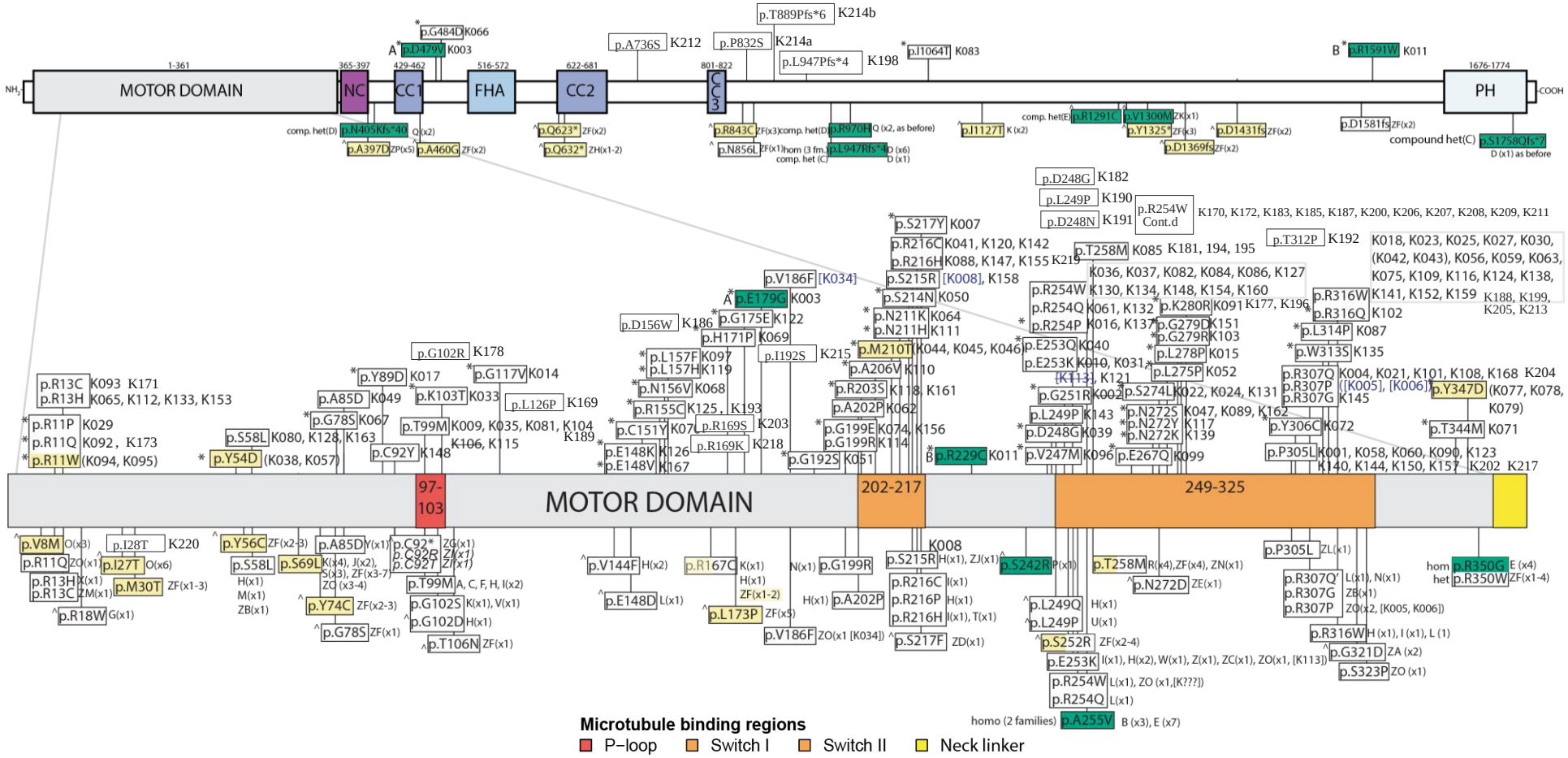
KIF1A protein

Molecular motor protein in the nervous system

Transports neuronal cargo in axons & dendrites along microtubules



KIF1A Variants

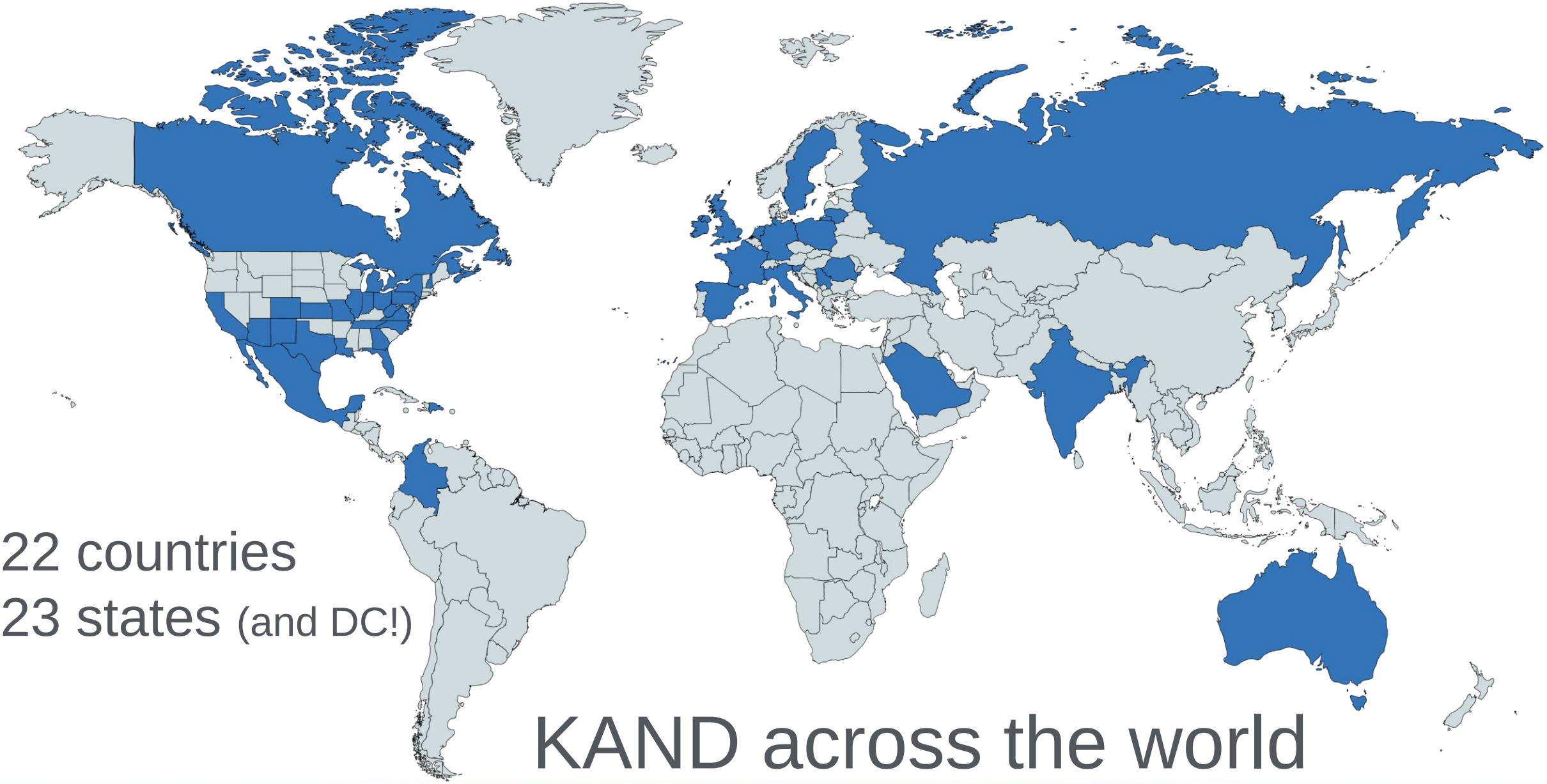


Study eligibility is based upon KIF1A genetics

- Genetic test report is reviewed for eligibility
- Consent obtained online

Methods: data collection

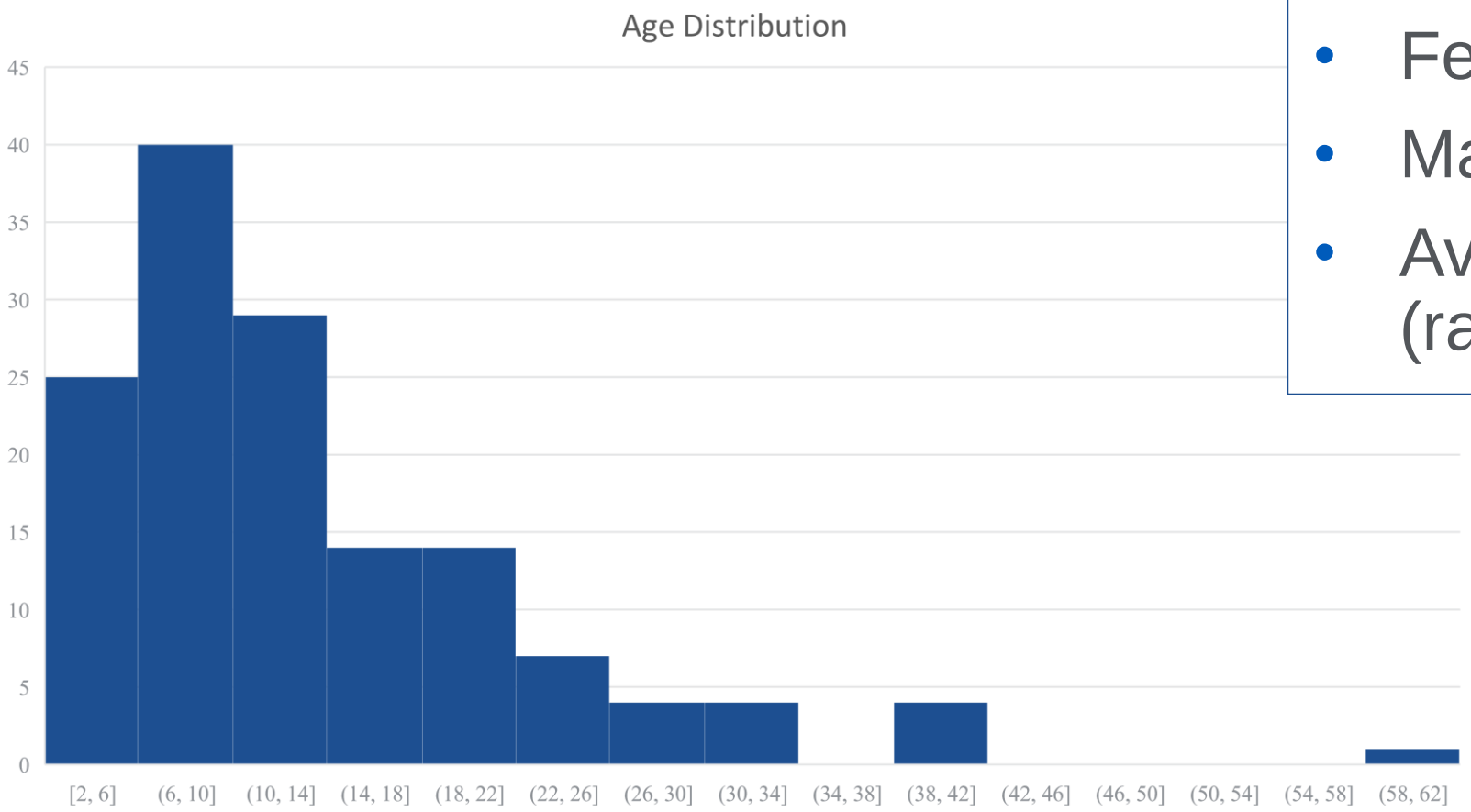
- Initial medical history interview via phone/online
- Medical records collected (including genetic test, MRI and EEG data)
- Parent or caregiver completes Vineland Adaptive Behavior Scales *(English/Spanish speakers only)*
  - Second edition previously completed via call
  - Third edition now completed online



22 countries
23 states (and DC!)

KAND across the world

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)

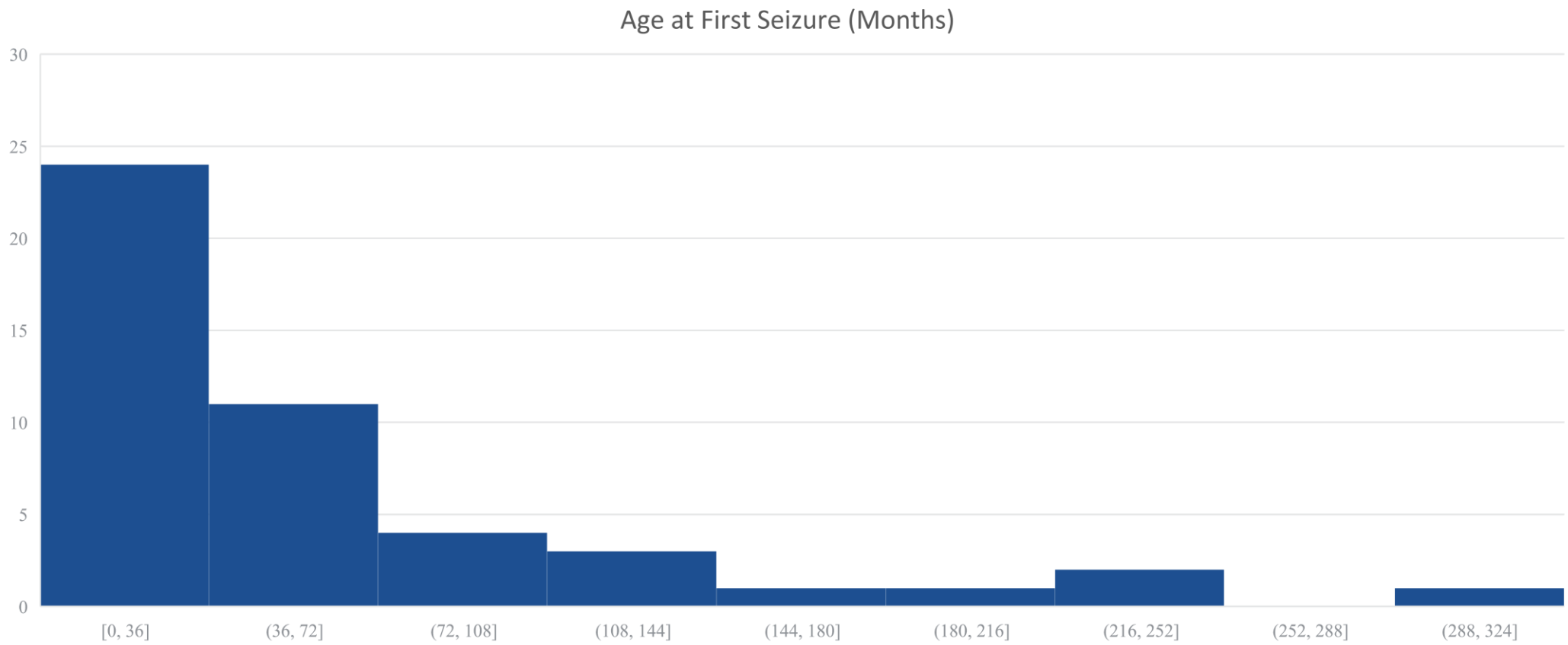
Hypertonia/spasticity: 75% (106/142)

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)



Seizures and epilepsy: details

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)

Condition	Prevalence
Optic Nerve Atrophy	61 (43%)
Strabismus	33 (23%)
Cortical vision loss	23 (16%)
Corrective lenses	54 (38%)
Cataracts	11 (8%)
Depth perception issue	10 (7%)

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

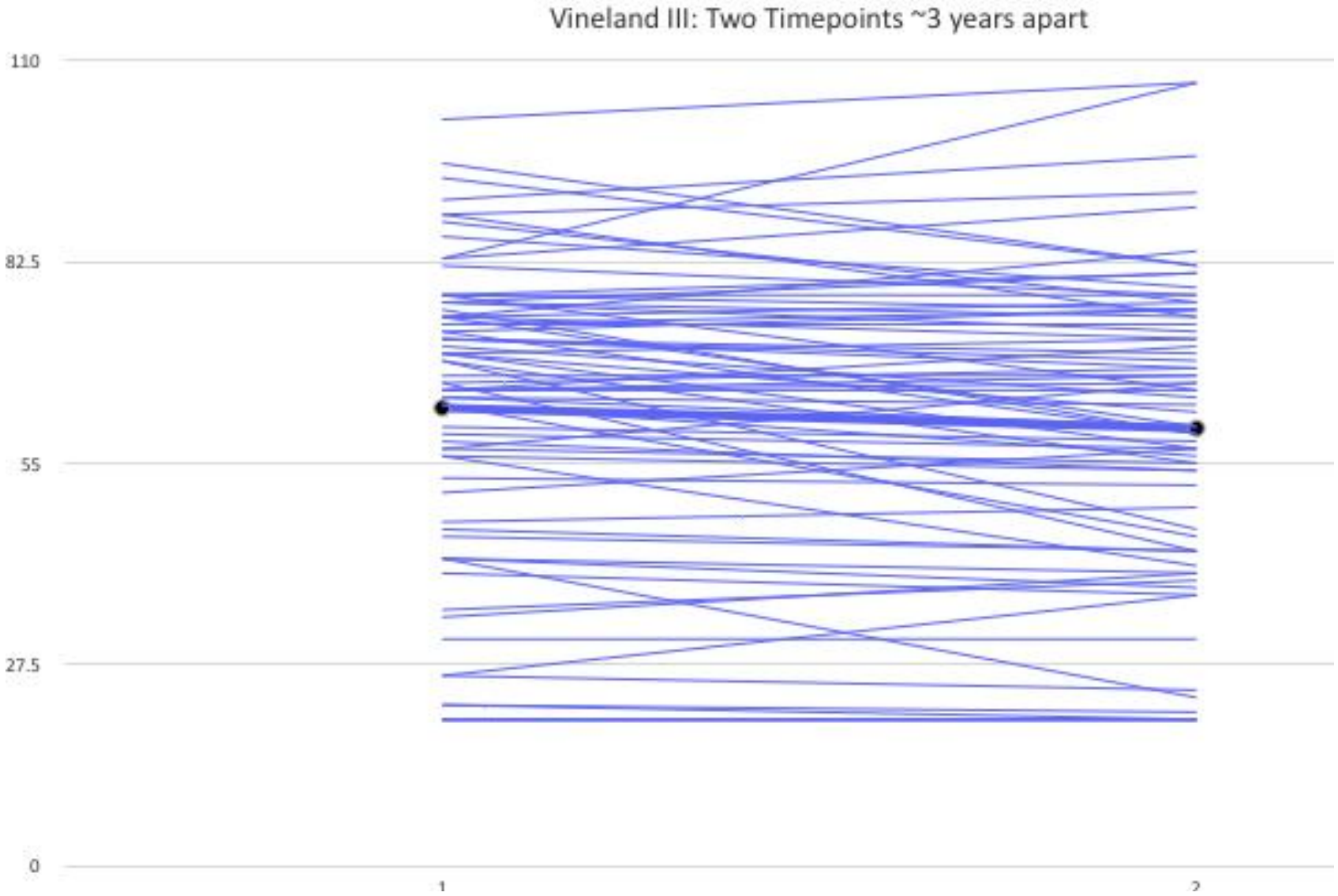
Difficulty regulating temperature

Sleep issues

Loss of Function Data

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

- 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!