What We've Learned from the KAND Natural History Study

Speaker: Lia Boyle, Chung Lab, Columbia University

August 16, 2019

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*

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

Why a natural history study?

- Begin with the end in mind!

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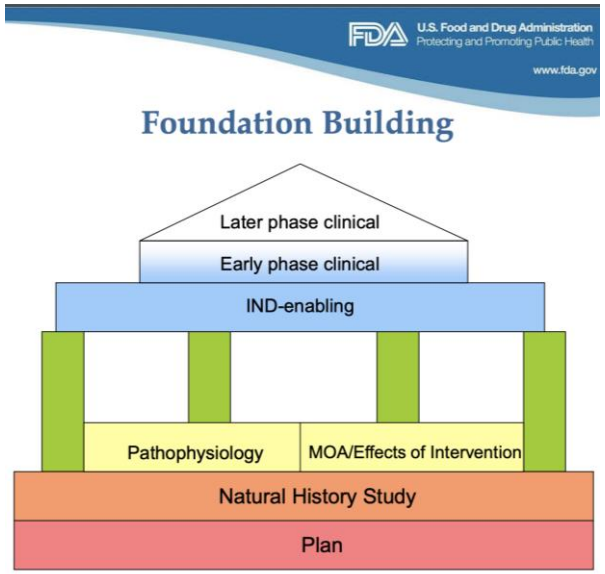

- Begin with the end in mind!
- Foundational for drug development
- "The top reason why rare disease development programs fail at FDA is the lack of natural history information" – Christopher Austin, head of NIH's National Center for Advancing Translational Sciences*

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

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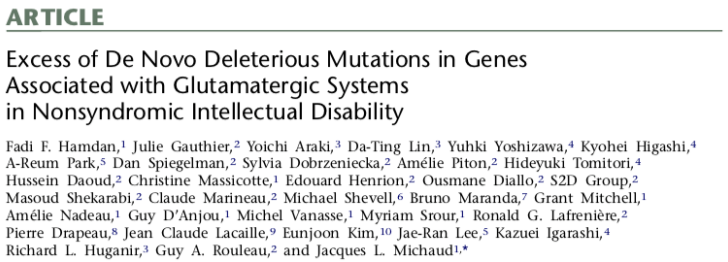
What we knew

First *KIF1A* patients: 2011



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

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- Single *KIF1A* case
- Hypotonia, spasticity, and intellectual disability
- Spontaneous p.T99M mutation

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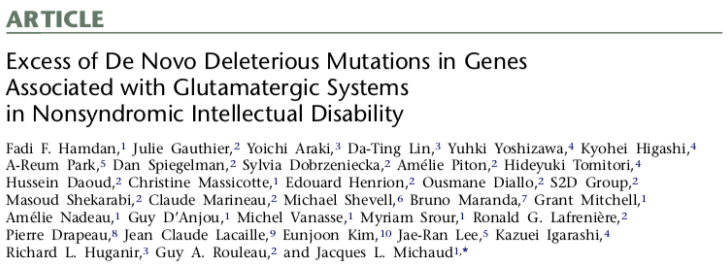
MRD9



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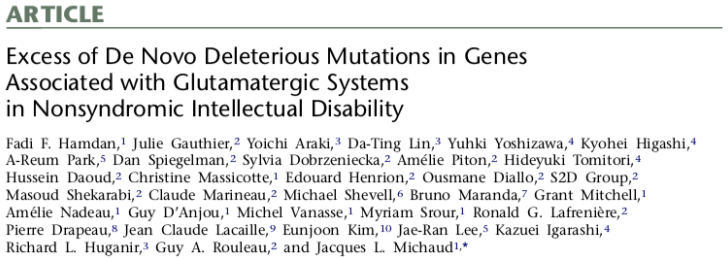

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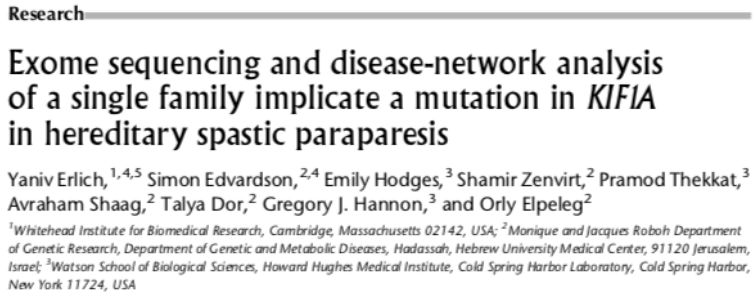

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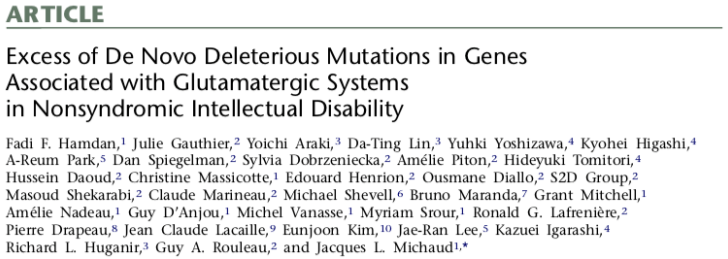

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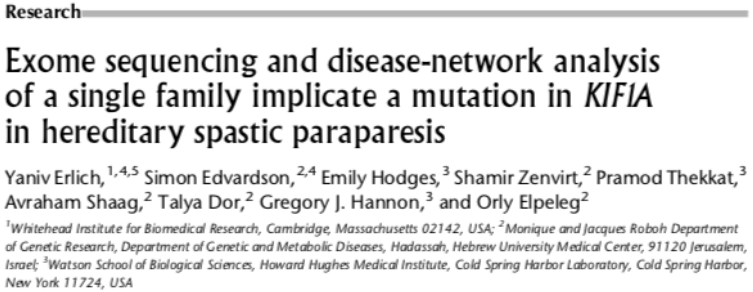

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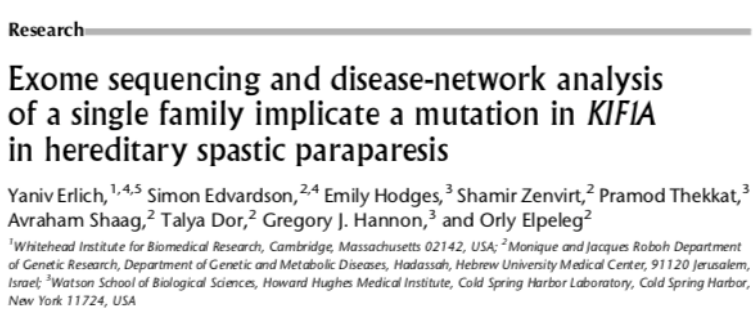

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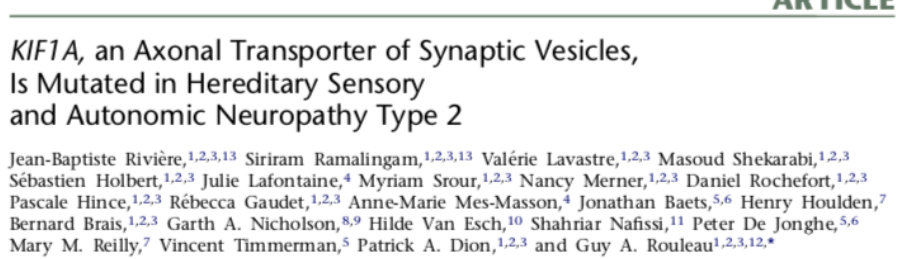

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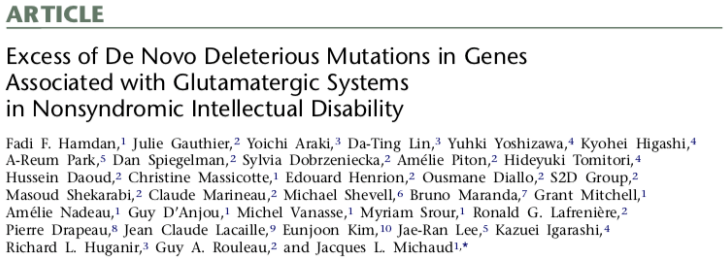

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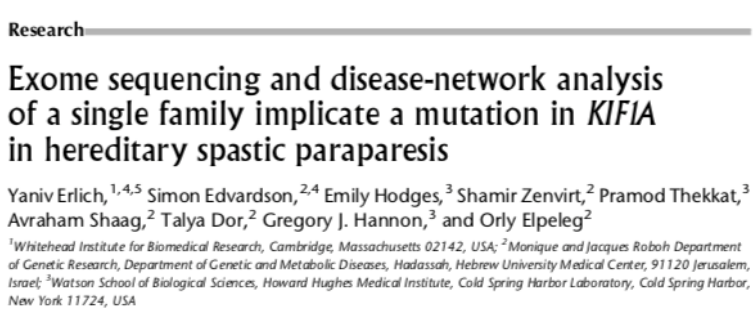

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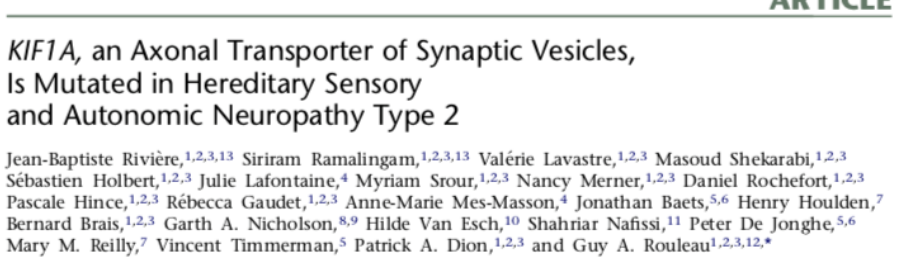

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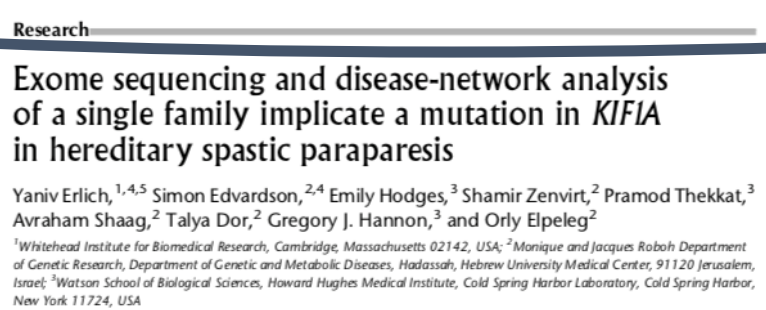

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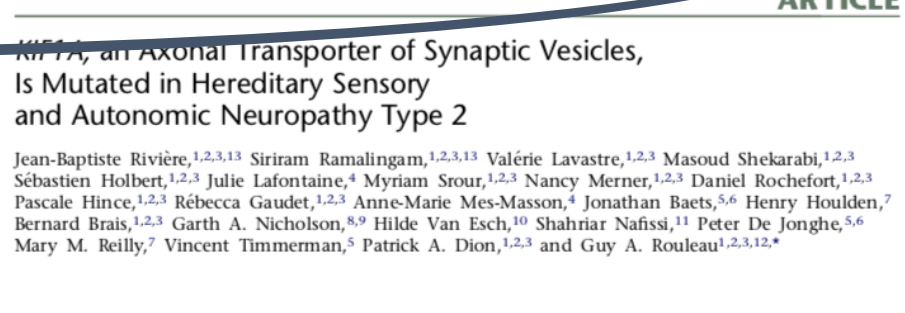

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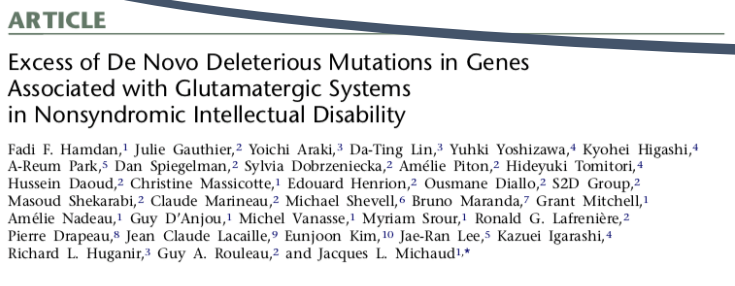

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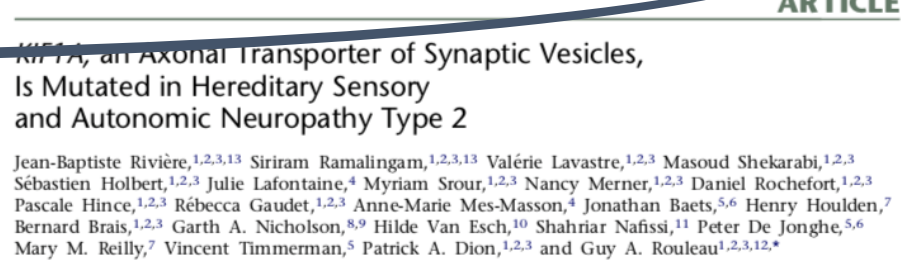

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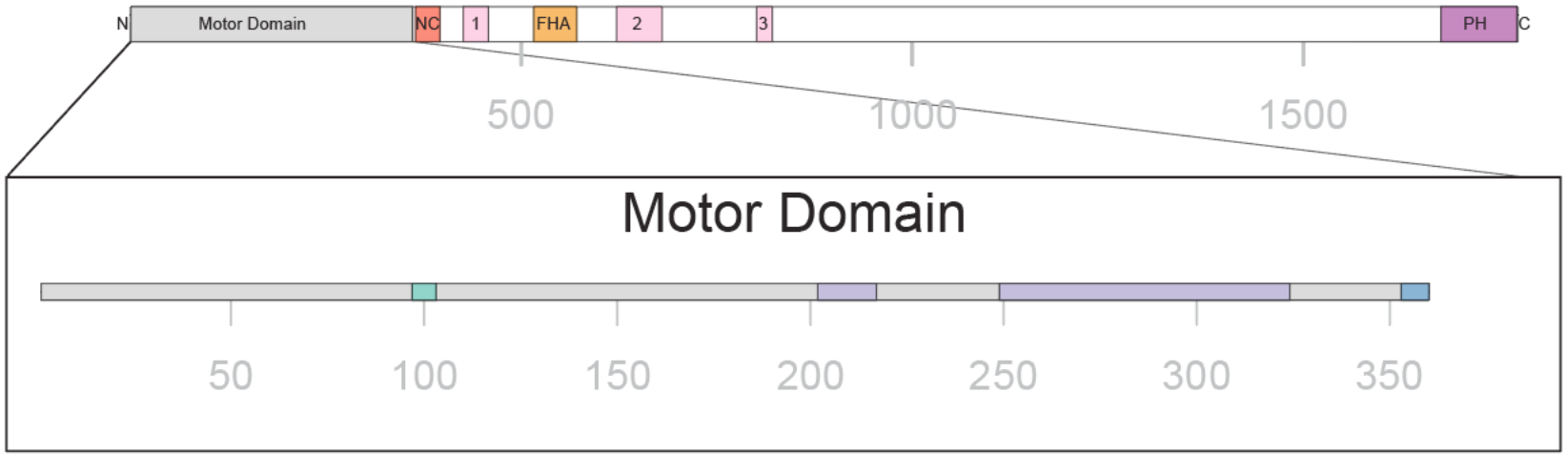
KAND

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

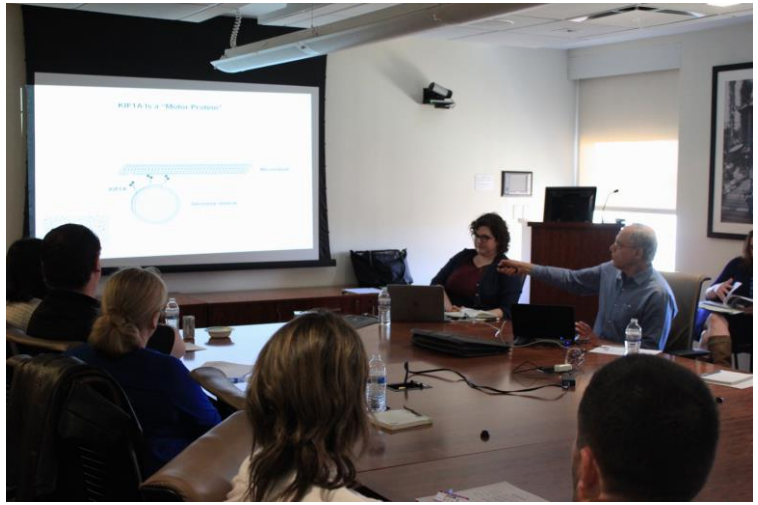
Neck coil Coiled coil Forkhead associated Pleckstrin homology

Microtubule binding regions

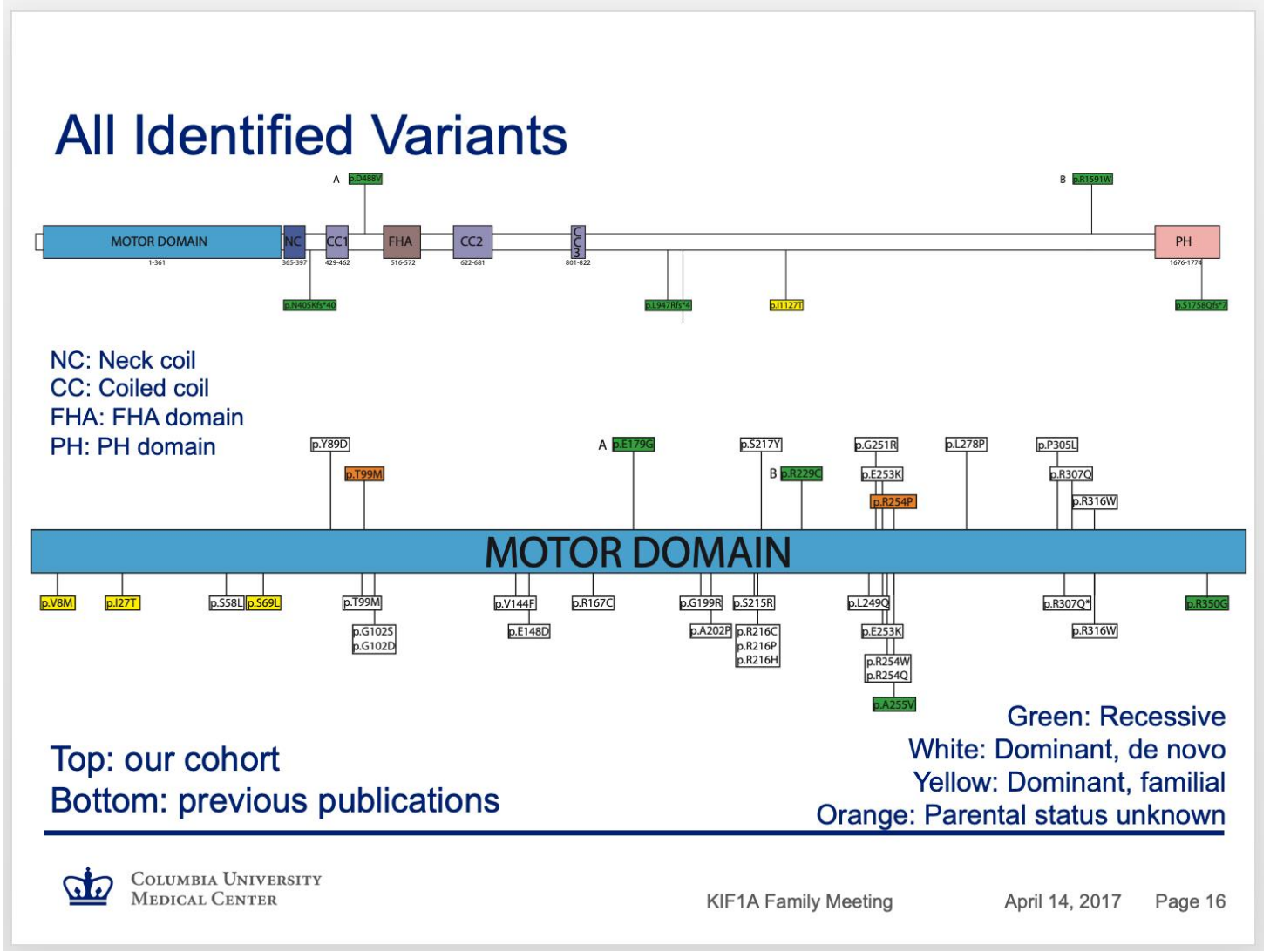
P−loop Switch I Switch II Neck linker

KIF1A Family Meeting 2017

- More than 30 people (10+ in person, 20+ online)



KAND then


All Identified Variants
A
p.D488V
B
p.R1591W
MOTOR DOMAIN
NC
CC1
FHA
CC2
CC3
PH
1-361
365-397
429-462
516-572
622-681
801-822
1676-1774
p.N405Kfs*48
p.L947Rfs*4
p.I1127T
p.S1758Qfs*7
NC: Neck coil
CC: Coiled coil
FHA: FHA domain
PH: PH domain
p.Y89D
p.T99M
A
p.E179G
p.S217Y
B
p.R229C
p.G251R
p.E253K
p.R254P
p.L278P
p.P305L
p.R307Q
p.R316W
MOTOR DOMAIN
p.V8M
p.I27T
p.S58L
p.S69L
p.T99M
p.G102S
p.G102D
p.V144F
p.E148D
p.R167C
p.G199R
p.A202P
p.S215R
p.R216C
p.R216P
p.R216H
p.L249Q
p.E253K
p.R254W
p.R254Q
p.A255V
p.R307Q*
p.R316W
p.R350G
Top: our cohort
Bottom: previous publications
Green: Recessive
White: Dominant, de novo
Yellow: Dominant, familial
Orange: Parental status unknown
Columbia University
Medical Center
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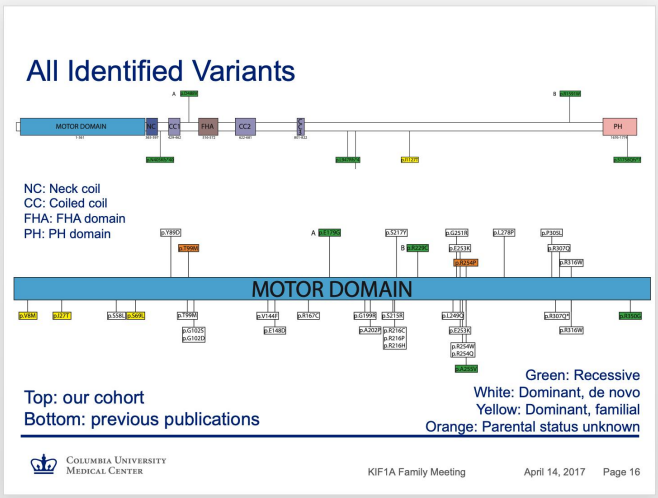
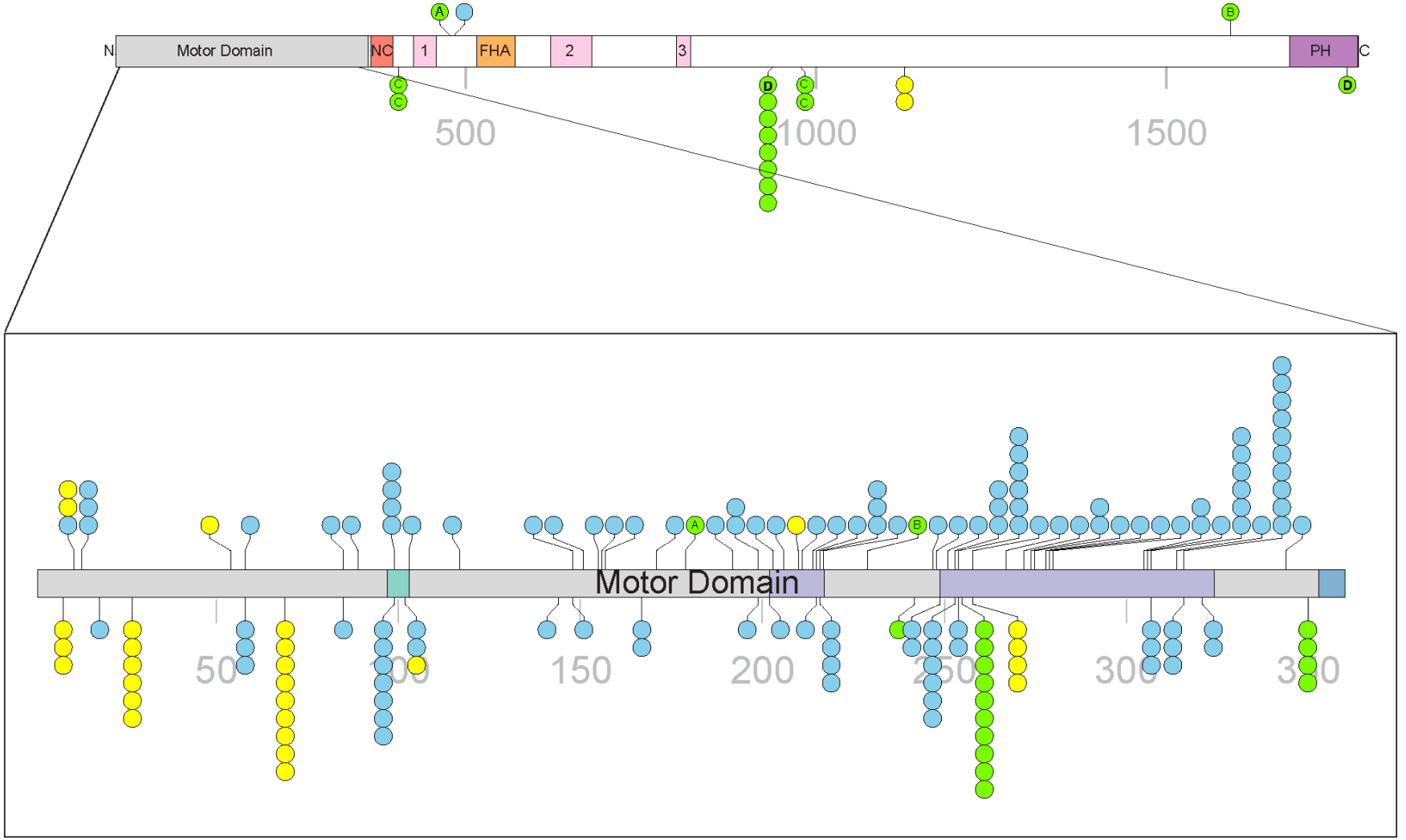
KAND now



Yellow: inherited, dominant
Green: inherited, recessive



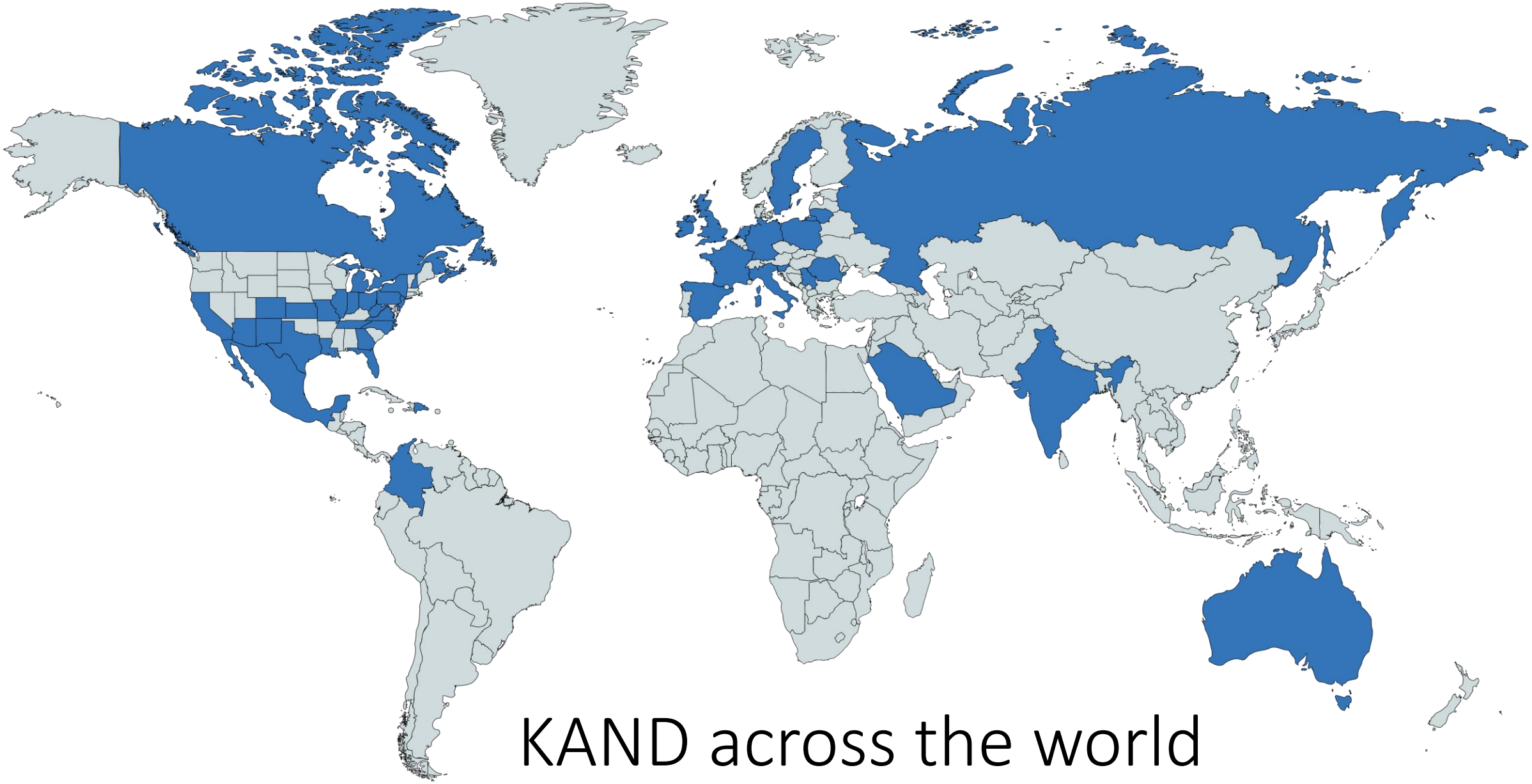
What we’ve learned

Methods: study enrollment

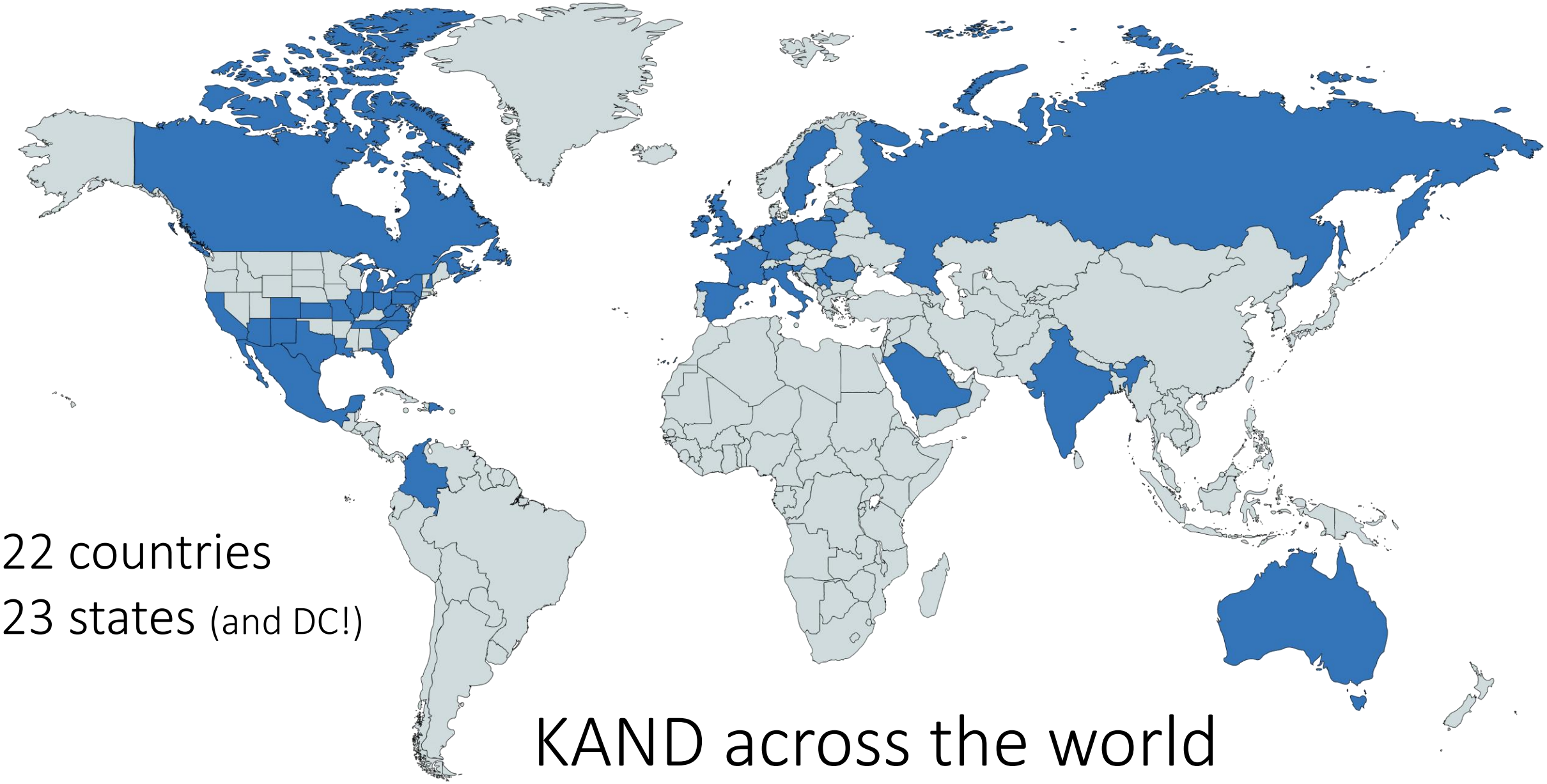
- Potential participant reaches out to us
- Initial information collected to determine eligibility
- Variants reviewed by researchers, eligible individuals invited to participate
- Study described in detail, consent obtained in person or online

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

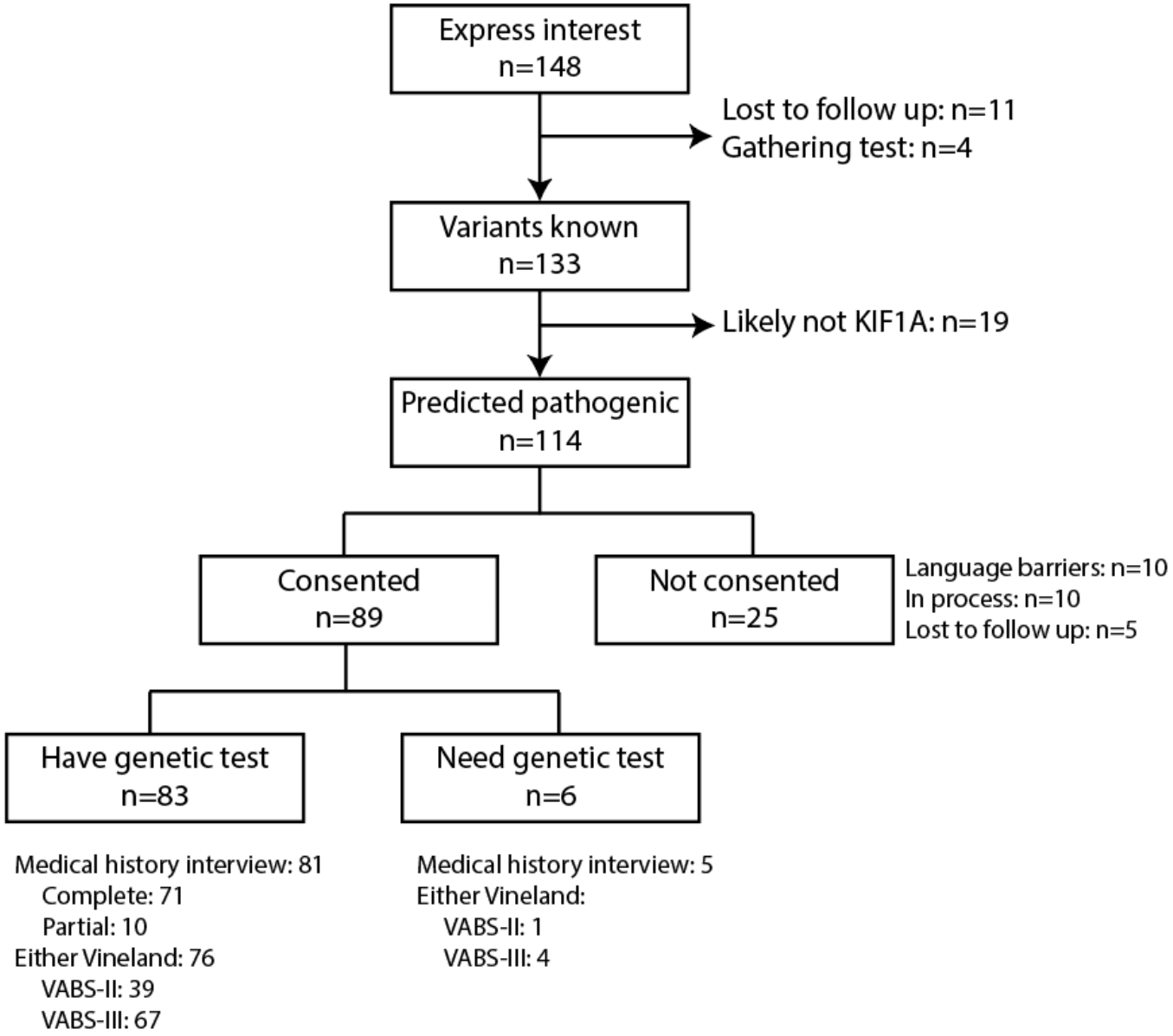


22 countries

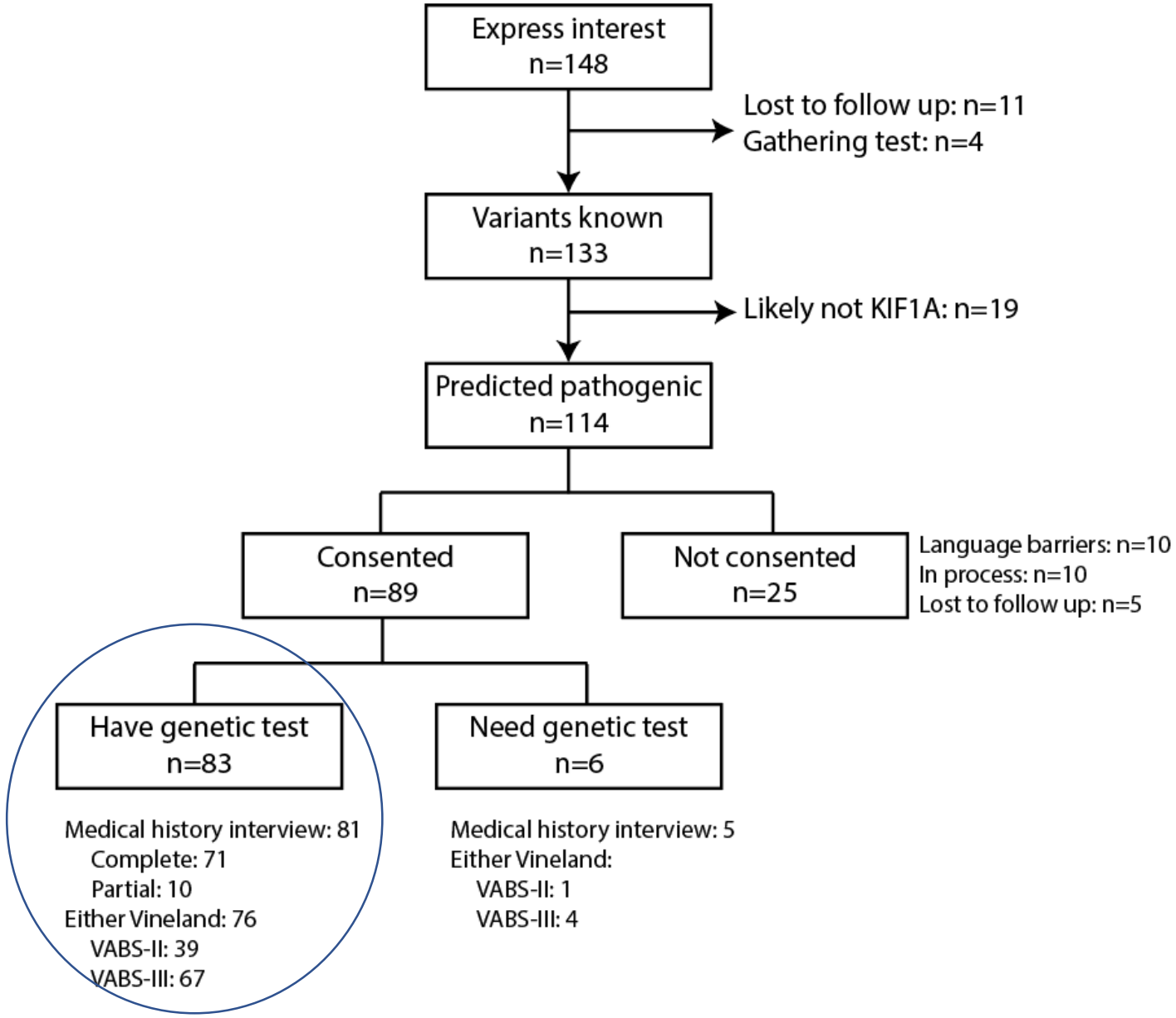
23 states (and DC!)

KAND across the world

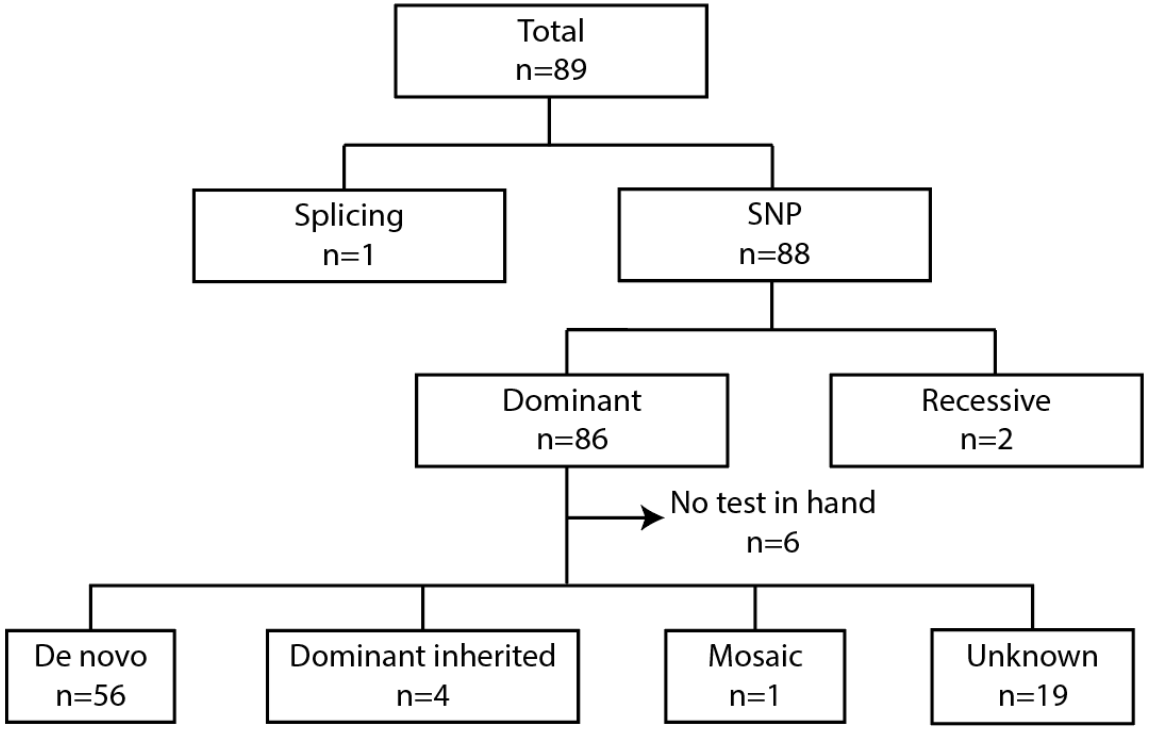
Study enrollment



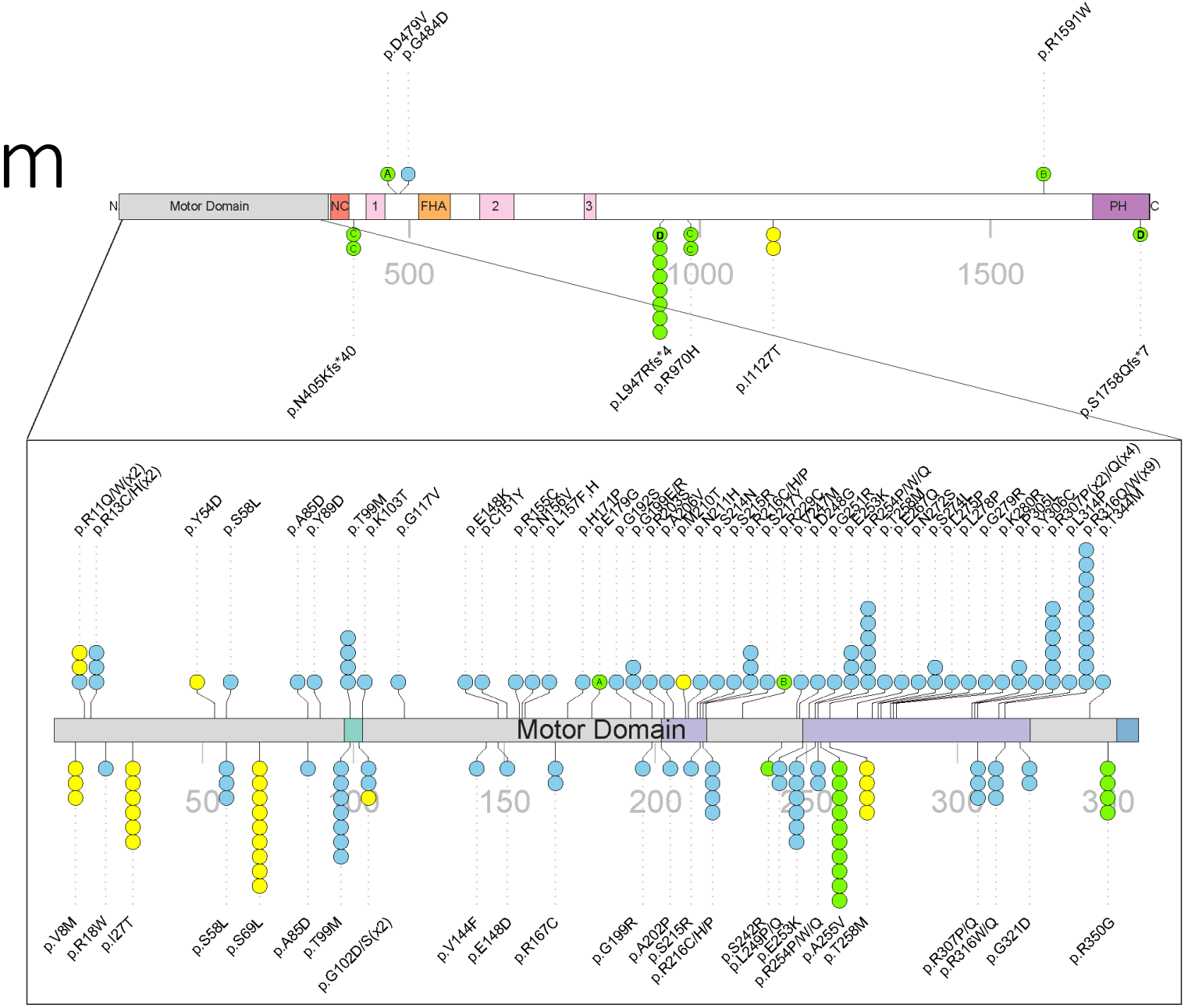
Study enrollment



Mutation type breakdown



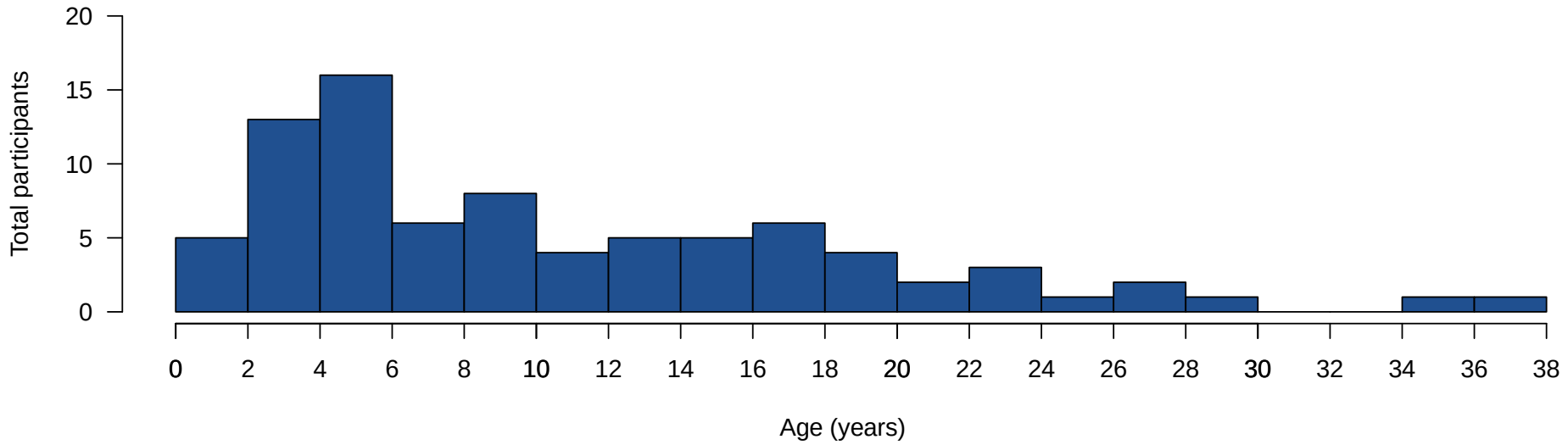
Mutation diagram



Yellow: inherited, dominant
Green: inherited, recessive

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)

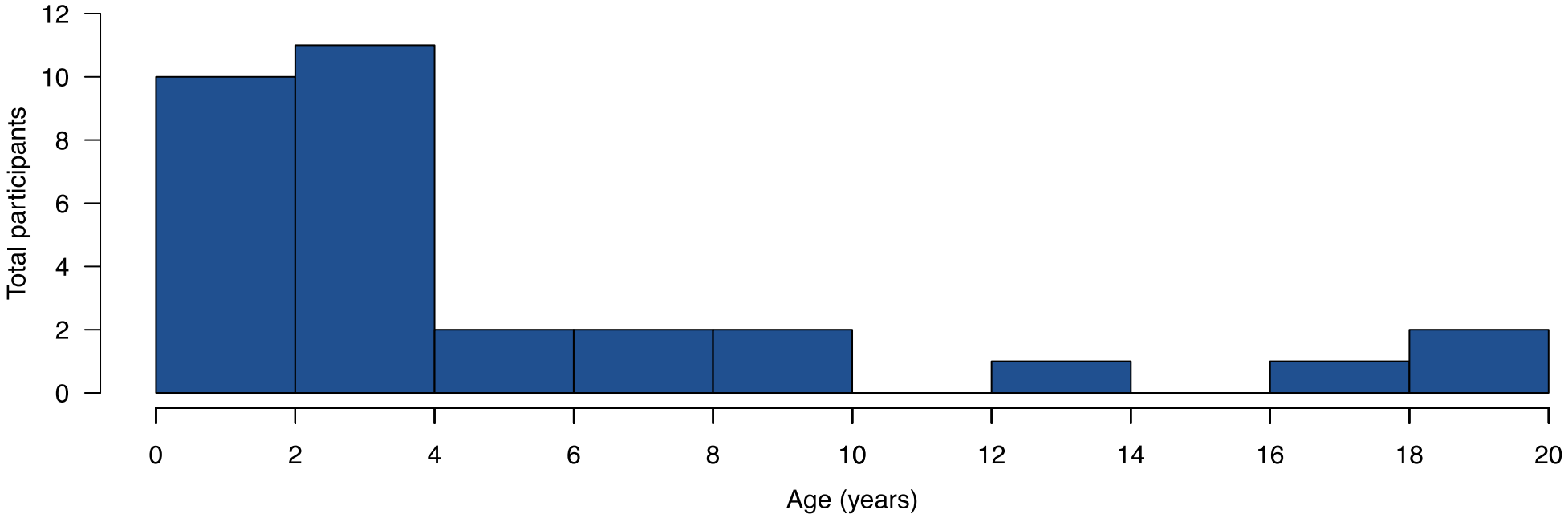
Seizures and epilepsy: an overview

- 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)

Seizures and epilepsy: details

- 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)

Seizures and epilepsy: details

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- Treatment refractory: 14% (5/35)

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 collosum: 11% (8/74)
- Cerebral atrophy: 5% (4/74)
- Other reported abnormalities: 32% (24/74)

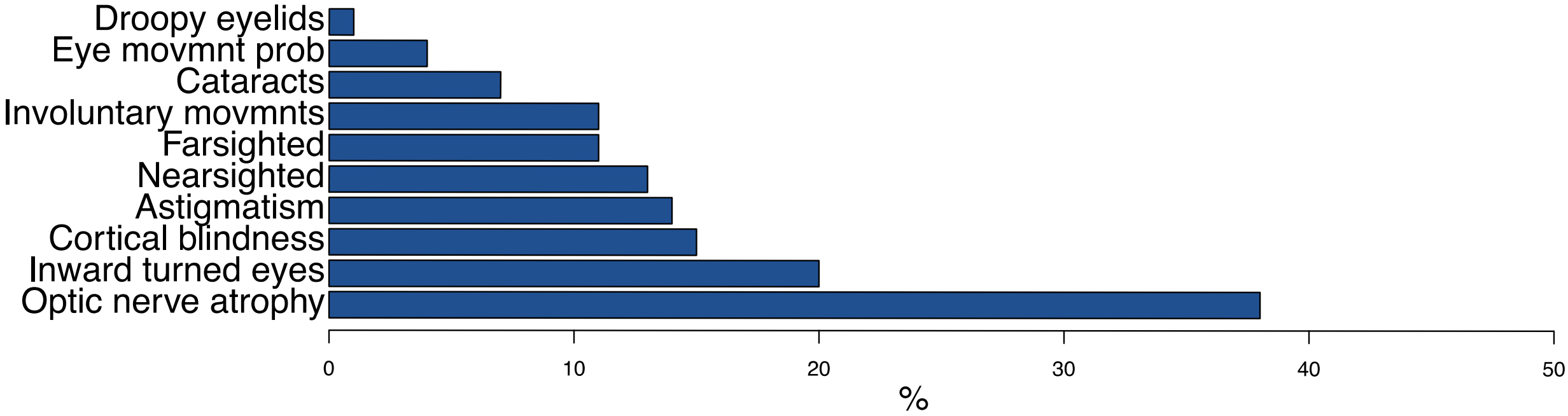
Neuroimaging details (changes over time)

- Cerebellar atrophy most common: 35% (26/74)
- Abnormalities of the corpus collosum: 11% (8/74)
- Cerebral atrophy: 5% (4/74)
- Other reported abnormalities: 32% (24/74)

- 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

- 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

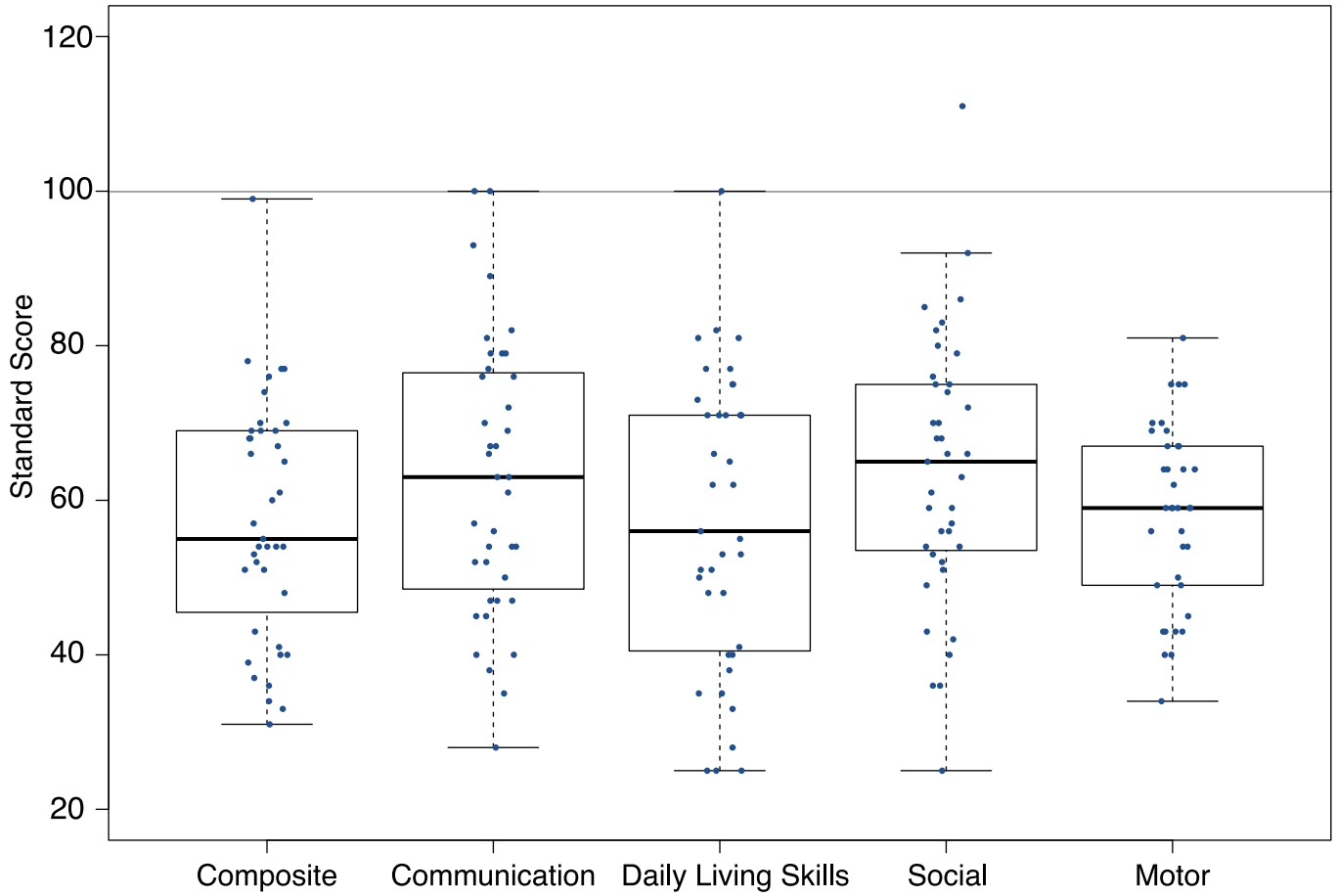
Additional findings

- 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

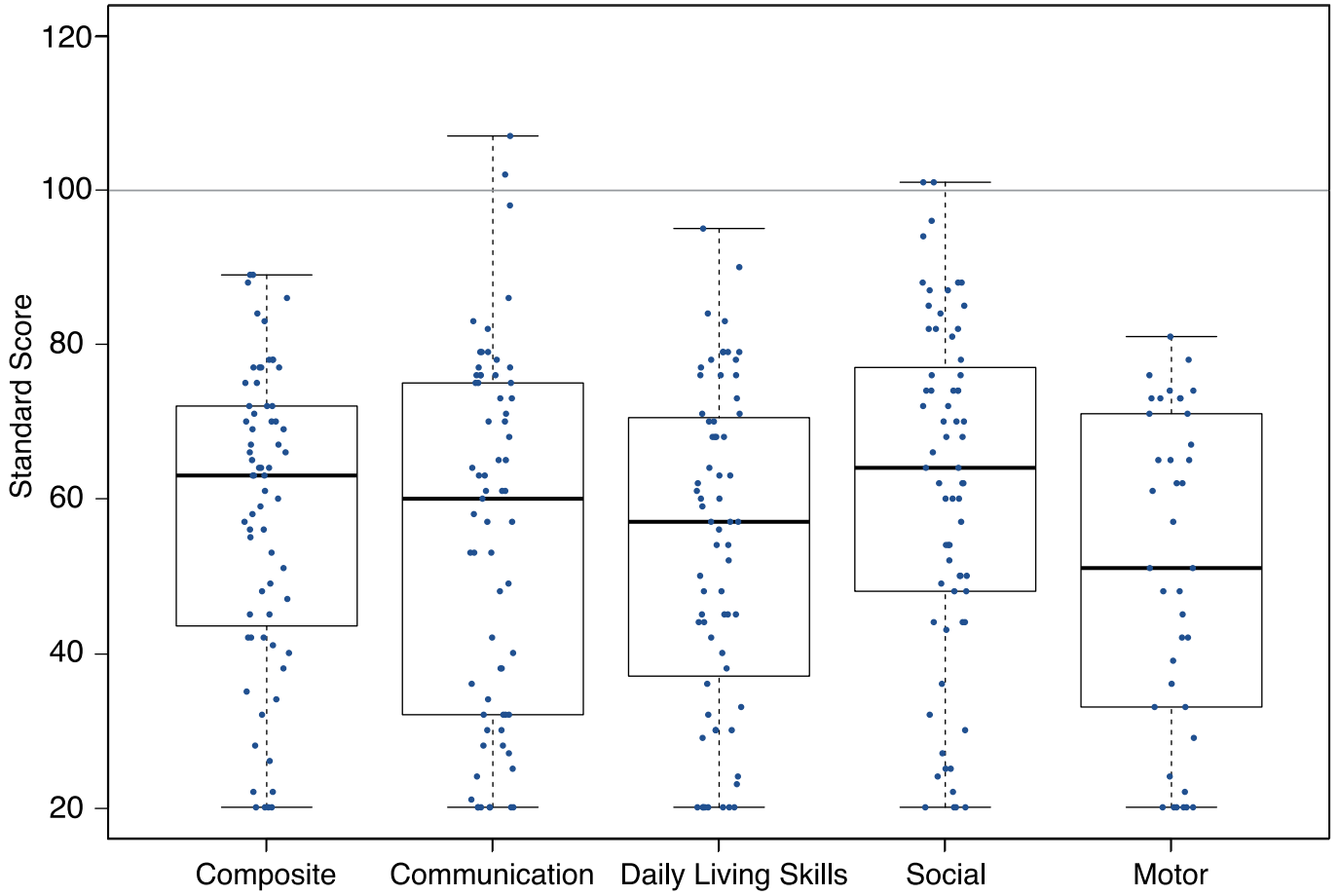
- Increased prevalence of autism, obsessive compulsive behavior and anxiety
- Increased pain tolerance
- Small, cold hands and feet
- Difficulty regulating temperature
- Sleep issues

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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Charles LeDuc

Yufeng Shen

Xiao Fan

Our collaborators

Thanks to *you*, our amazing KAND patients and families!

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