Columbia University Medical Center

KIF1A Family Meeting

Friday, April 14th, 2017

Agenda

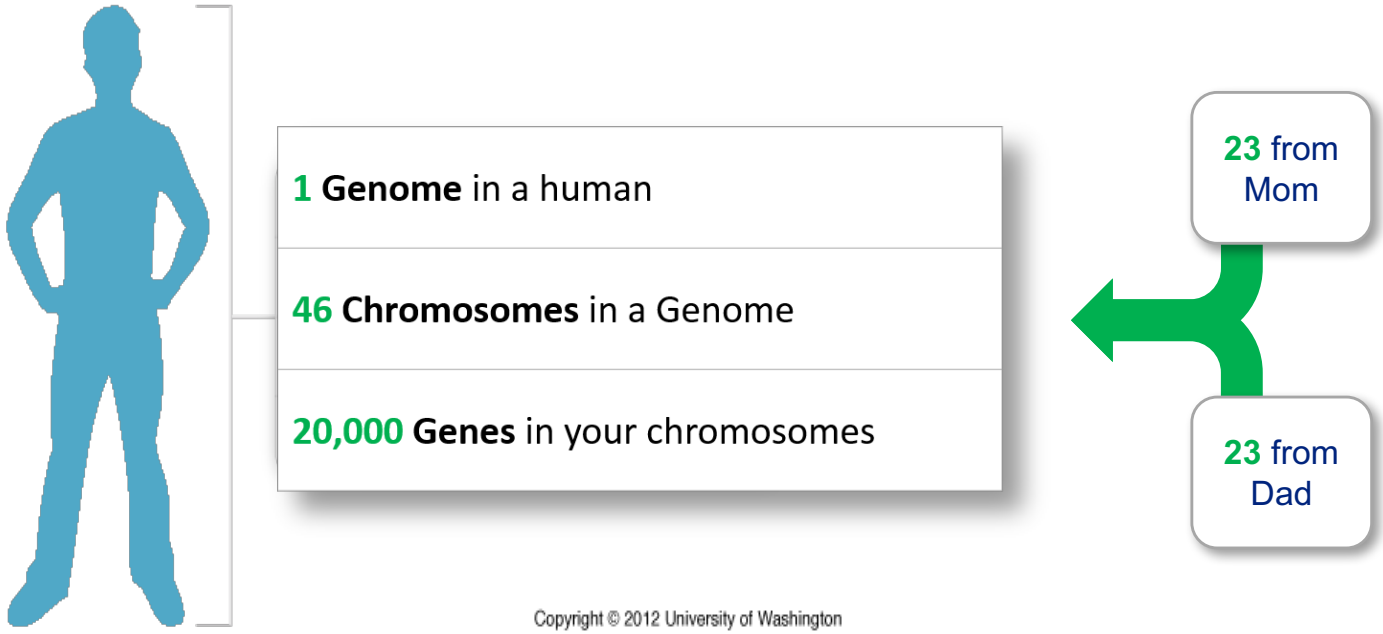
11:00pm	Welcome, Genetics 101	Wendy Chung
11:10pm	Review of *KIF1A* family responses	Lia Boyle
11:40pm	Answering questions about eye issues with *KIF1A*	Steven Brooks
12:00pm	Answering questions about neurological issues with *KIF1A*	Jennifer Bain
12:30pm	What does *KIF1A* do?	Richard Vallee
1:00pm	Open discussion about future research directions and priorities	

Welcome
Genetics 101

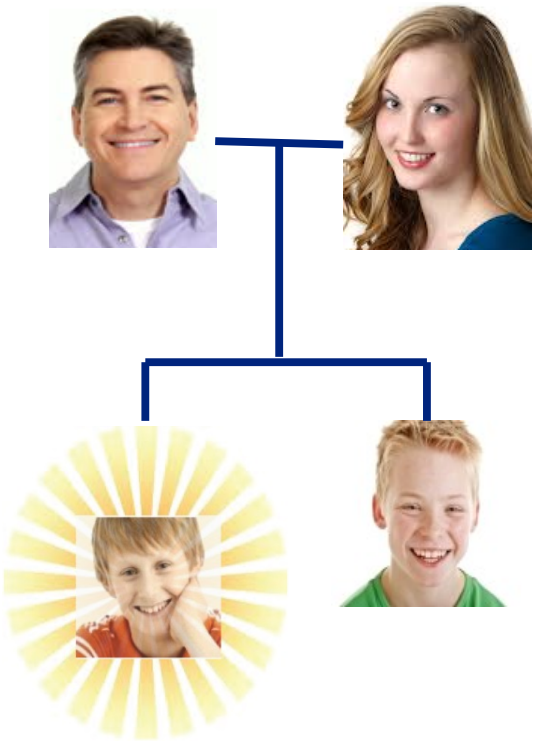
Wendy Chung, MD, PhD

Clinical Geneticist

Our Genome



Not all Genetic Conditions Run in Families
De novo mutations are common children with neurodevelopmental problems



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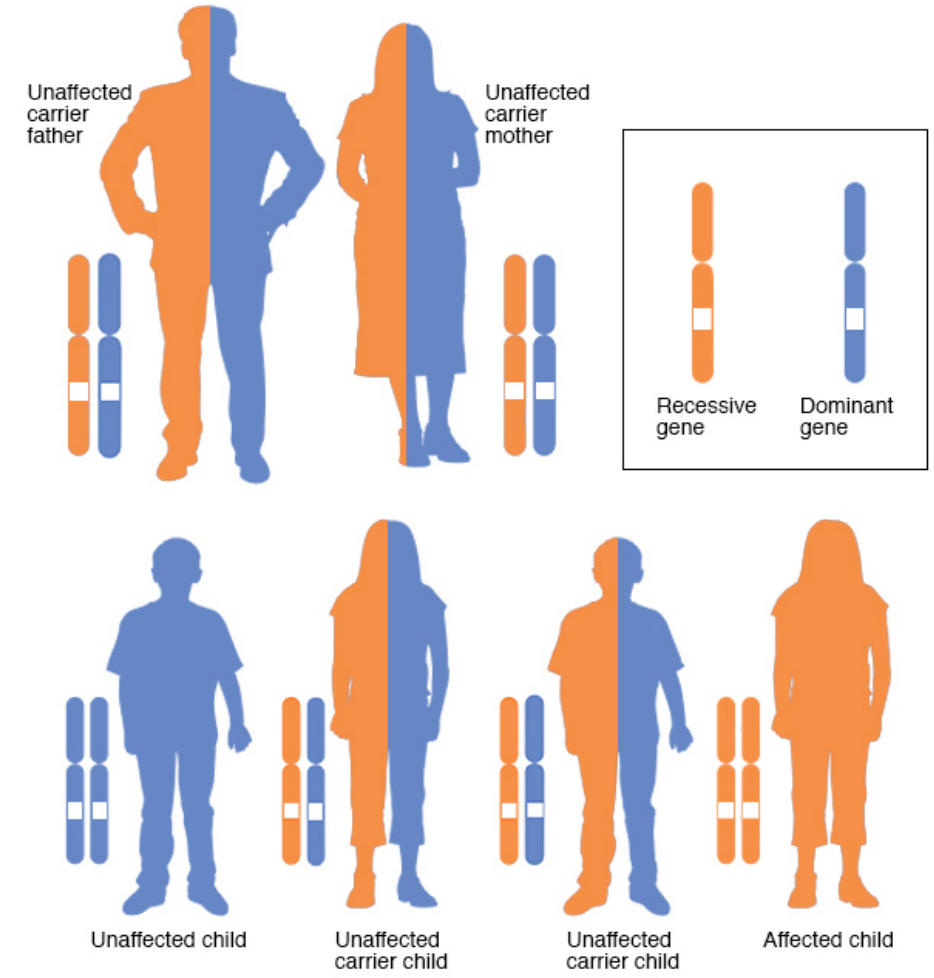
When do de novo mutations occur?

- In the egg
- In the sperm
- At or shortly after conception
- No way to know
- Recurrence risk of 1% in future pregnancies

Recessive condition: 25% recurrence for parents



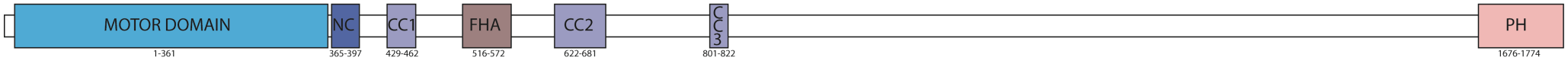
A Clinical Picture of Individuals with *KIF1A* Variants

Lia Boyle

Published Studies

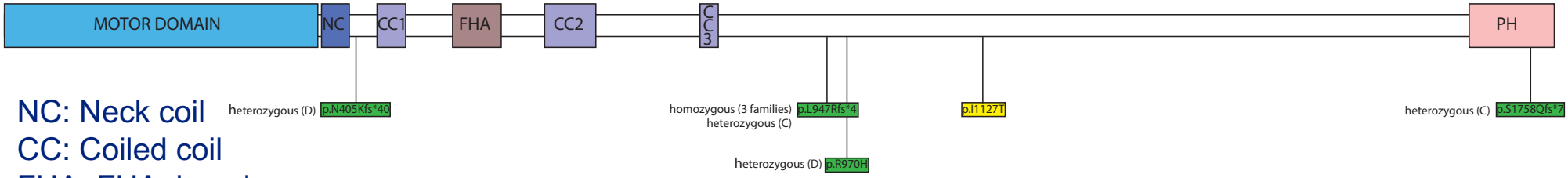
- The first individual with a known *KIF1A* variant was identified in 2011
- Since then, 16 papers have been published describing a total of 84 individuals from 49 families throughout the world
- 30 different genetic variants identified
- Specific clinical findings are available 66 individuals

Understanding the layout of the gene

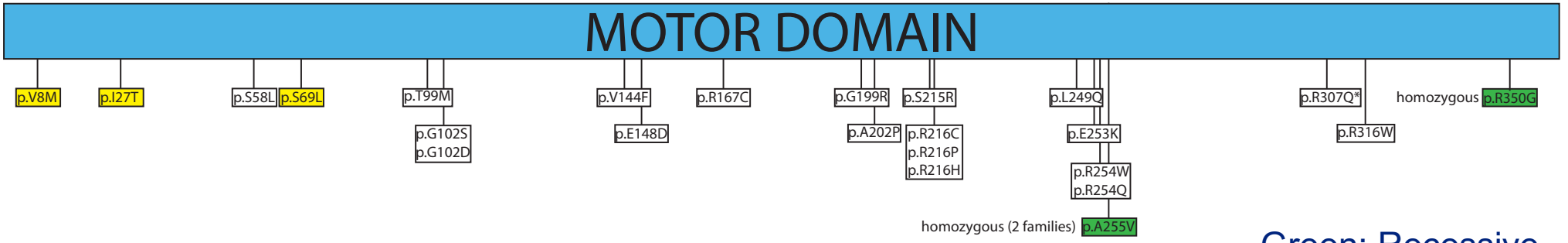


Motor domain (1-361)
NC: Neck coil (365-397)
CC1: Coiled coil 1 (429-462)
FHA: FHA domain (516-572)
CC2: Coiled coil 1 (622-681)
CC3: Coiled coil 1 (801-822)
PH: PH domain (1676-1774)

Variants Identified in Published Studies



NC: Neck coil
CC: Coiled coil
FHA: FHA domain
PH: PH domain



Green: Recessive
White: Dominant, de novo
Yellow: Dominant, familial

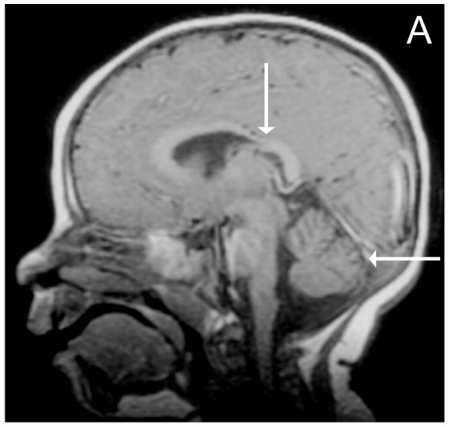
Clinical Information from Published Studies

	Dominant, Sporadic N=31	Dominant, Familial N=10	Recessive, N=25	Total N=66
Unique variants	19	5	7	31
Mean age years (SD)	11(8.5)	40 (22.3)	27(16.1)	
Sex	M: 12, F: 19	M: 6, F: 4	M: 12, F: 13	M: 30, F: 36
Developmental delay	100% (31/31)	0% (0/10)	16% (4/25)	53% (35/66)
Hypotonia	39% (12/31)	0% (0/10)	16% (4/25)	30% (20/66)
Spasticity	77% (24/31)	100% (10/10)	100% (25/25)	89% (59/66)
Seizures	29% (9/31)	0% (0/10)	0% (0/25)	14% (9/66)
Any optic findings Optic nerve change	74% (23/31) 58% (18/31)	10% (1/10) 0% (0/10)	12% (3/25) 0% (0/25)	41% (27/66) 27%(18/66)
Abnormal MRI Cerebellar atrophy	86% (25/29) 75% (22/29)	25% (1/4) 0% (0/4)	36% (4/11) 18% (2/11)	68% (30/44) 55% (24/44)
Sensory neuropathy	48% (15/31)	0% (0/10)	36% (9/25)	55% (24/66)

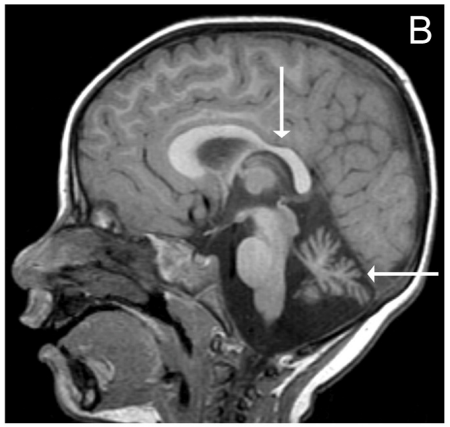
Some Examples of Imaging Findings

Patient 1

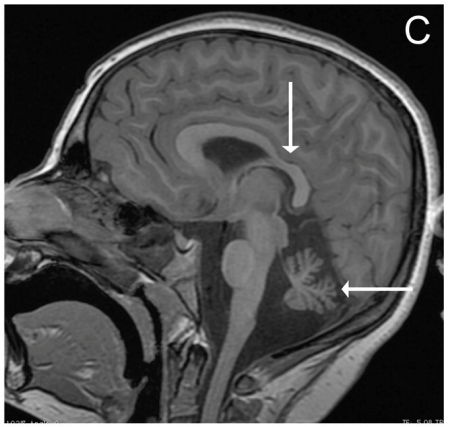
11 months



3.6 years

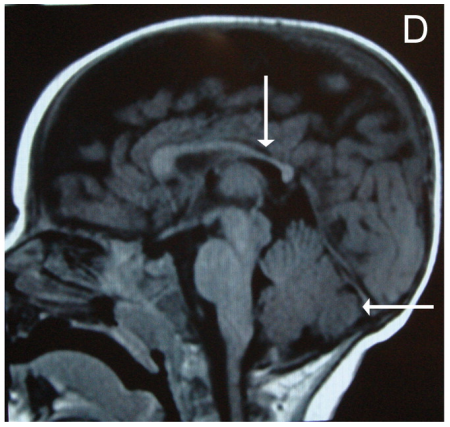


12.5 years

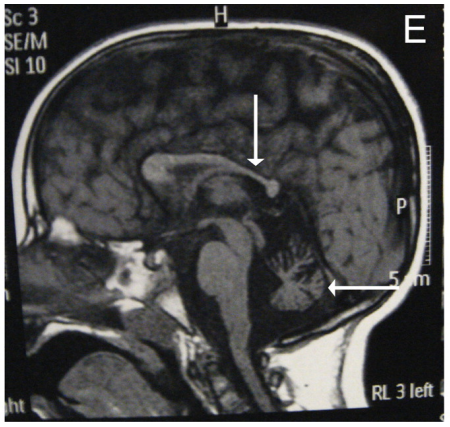


Patient 2

6 months



6 years



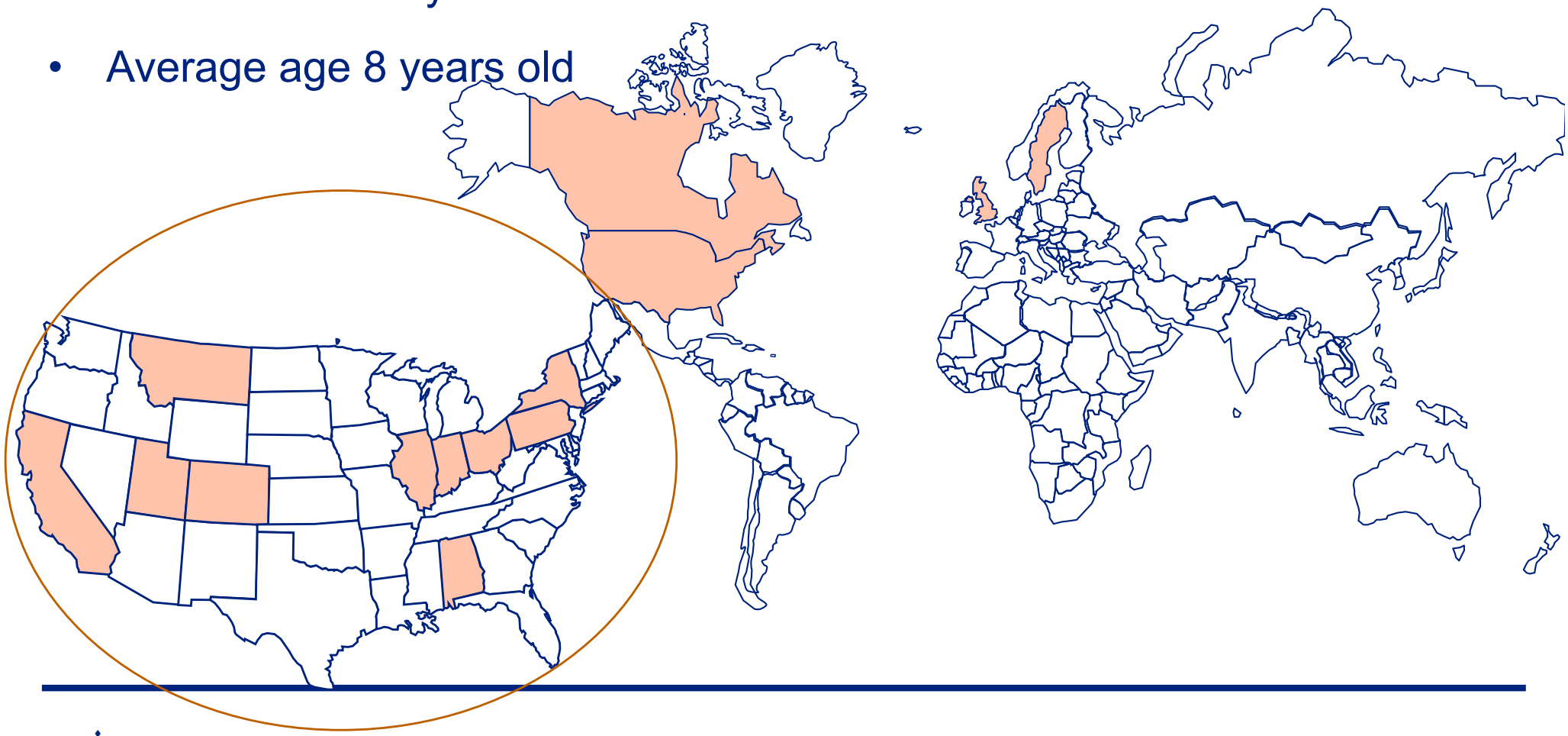
Hotchkiss, *Journal of Child Neurology* 31, 1114-1119.

Study Design

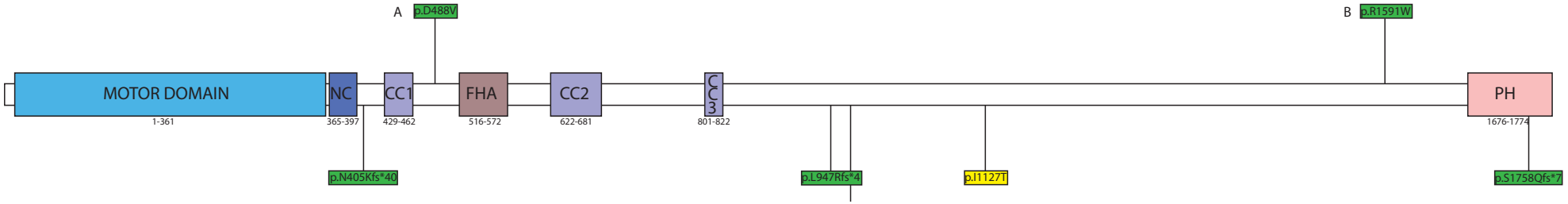
- Individuals with previously identified *KIF1A* mutations through clinical testing
- Recruitment largely through an existing family support group
  - A recruitment letter was shared on a private Facebook group
- Participating families took part in a two hour phone interview involving a detailed medical history as well as a structured developmental interview

Who is included?

- 14 individuals from 4 countries & 10 states
- 11 months to 20 years old
- Average age 8 years old



All Identified Variants



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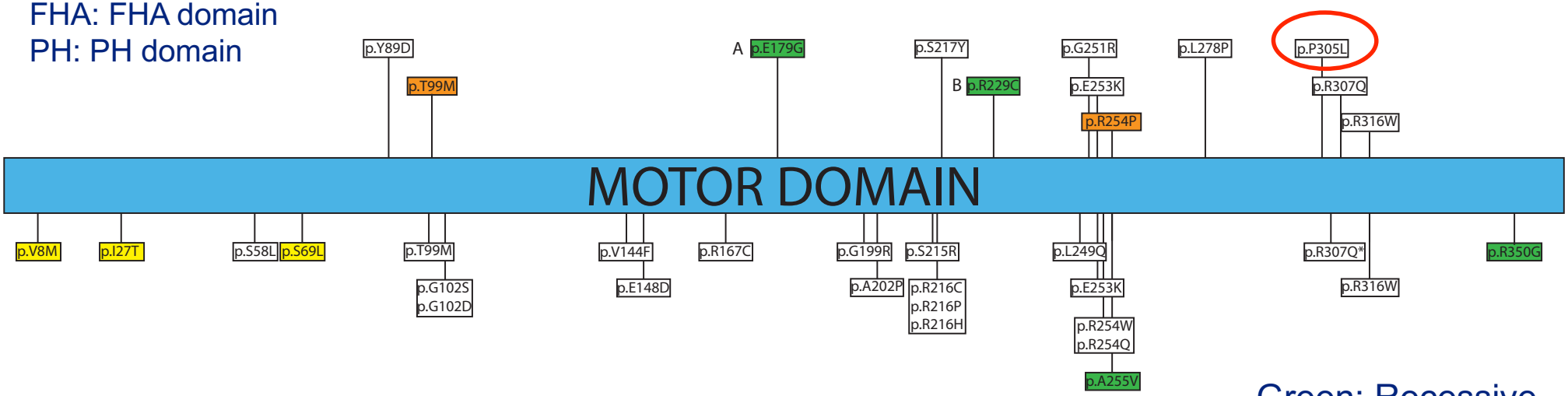


Top: our cohort
Bottom: previous publications

Green: Recessive
White: Dominant, de novo
Yellow: Dominant, familial
Orange: Parental status unknown

Groupings for Analysis

- Participants were grouped according to genetic status
- Group 1: Individuals with single, dominant mutations in motor domain
- Group 2: Individuals who have two mutations, one from each parent
- Group 3: Individuals of unknown genetic status

	Dominant N=10	Recessive N=2	Unknown N=2	Total N=14
Sex	M: 7 F: 3	M: 2 F: 0	M: 0 F: 2	M: 9 F: 5

Groupings for Analysis: Dominant

Variant	Inheritance	Seen before?
p.Y89D	De novo	Novel
p.T99M	Parental testing unavailable	Seen de novo in 7 individuals
p.S217T	De novo	Novel
p.G251R	De novo	Novel
p.E253K	De novo	Seen de novo in 3 individuals
p.R254P	Parental testing unavailable	Novel, though p.R254W and p.R254Q seen de novo
p.L278P	De novo	Novel
p.P305L	De novo	Novel
p.R307Q	De novo	Seen de novo in 2 individuals
p.R316W	De novo	Seen de novo in 1 individual

Groupings for Analysis: Recessive

Variant	Inheritance	Seen before?
p.E179G; p.D479V	Maternal; Paternal	Both novel
p.R229C; p.R1490W	Maternal; Paternal	Both novel

Neurological Features

	Dominant N=10	Recessive N=2	Unknown N=2	Total N=14
Hypotonia	90% (9/10)	100% (2/2)	50% (1/2)	86% (12/14)
Hypertonia	60% (6/10)	50% (1/2)	100% (2/2)	64% (9/14)
Seizures	60% (6/10)	100% (2/2)	100% (2/2)	71% (10/14)
Developmental delay	100% (10/10)	100% (2/2)	100% (2/2)	100% (14/14)
Abnormal MRI	40% (4/10)	50% (1/2)	100% (2/2)	50% (7/14)

Additional Seizure Findings

	Dominant N=10	Recessive N=2	Unknown N=2	Total N=14
Any seizures	50% (5/10)	100% (2/2)	100% (2/2)	64% (9/14)
Generalized Tonic Clonic	60%(3/5)	0% (0/2)	100% (2/2)	56% (5/9)
Absence	100% (5/5)	50% (1/2)	50%(1/2)	78% (7/9)

Eye Findings

	Dominant N=10	Recessive N=2	Unknown N=3	Total N=14
Any eye findings	90% (9/10)	100% (2/2)	100% (2/2)	93% (13/14)
Optic nerve change	70% (7/10)	0% (0/2)	100% (2/2)	64% (9/14)
Strabismus	10% (1/10)	100% (2/2)	0% (0/2)	21% (3/14)
Cataracts	10% (1/10)	50% (1/2)	0% (0/2)	14% (2/14)

Additional Findings

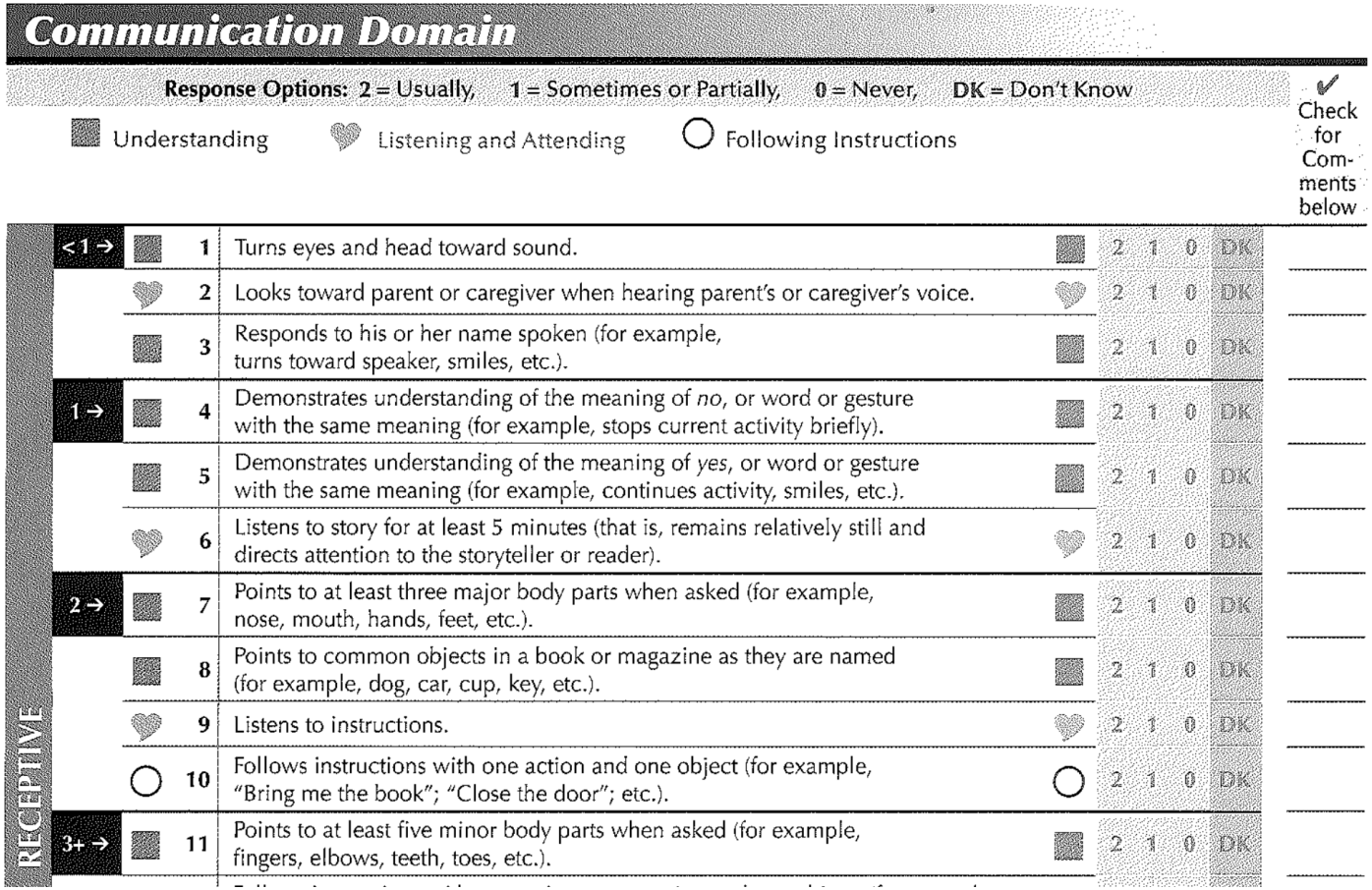
	Dominant N=10	Recessive N=2	Unknown N=2	Total N=14
Gastric reflux	50% (5/10)	100% (2/2)	100% (2/2)	64% (9/14)
Severe ear infections	20% (2/10)	50% (1/2)	0% (0/2)	21% (3/14)
Eczema	40% (4/10)	100% (2/2)	50% (1/2)	50% (7/14)
Genital abnormalities*	30% (3/10) M: 43% (3/7) F: 0% (0/3)	0% (0/2) M: 0% (0/2) F: 0% (0/0)	0% (0/2) M: 0% (0/0) F: 0% (0/2)	21% (3/14) M: 33% (3/9) F: 0% (0/5)
Urinary tract infections	10% (1/10) M: 0% (0/7) F: 33% (1/3)	0% (0/2) M: 0% (0/2) F: 0% (0/0)	100% (2/2) M: 0% (0/0) F: 100% (2/2)	21% (3/14) M: 0% (0/9) F: 60% (3/5)

**Genital abnormalities include micropenis, small scrotum, and undescended testicles*

Vineland Adaptive Behavior Scales

- Adaptive behavior: the performance of daily activities required for personal & social sufficiency
  - Age related
  - Evaluated in a social context
  - Modifiable
  - Defined by typical performance, *not* ability
- The Vineland Adaptive Behavior Scale (Vineland) is a structured phone interview
- Parents are asked about areas of functioning and whether a child does something never, sometimes, or usually
- Limitations: verbal ability, vision

Vineland Adaptive Behavior Scales



Communication Domain

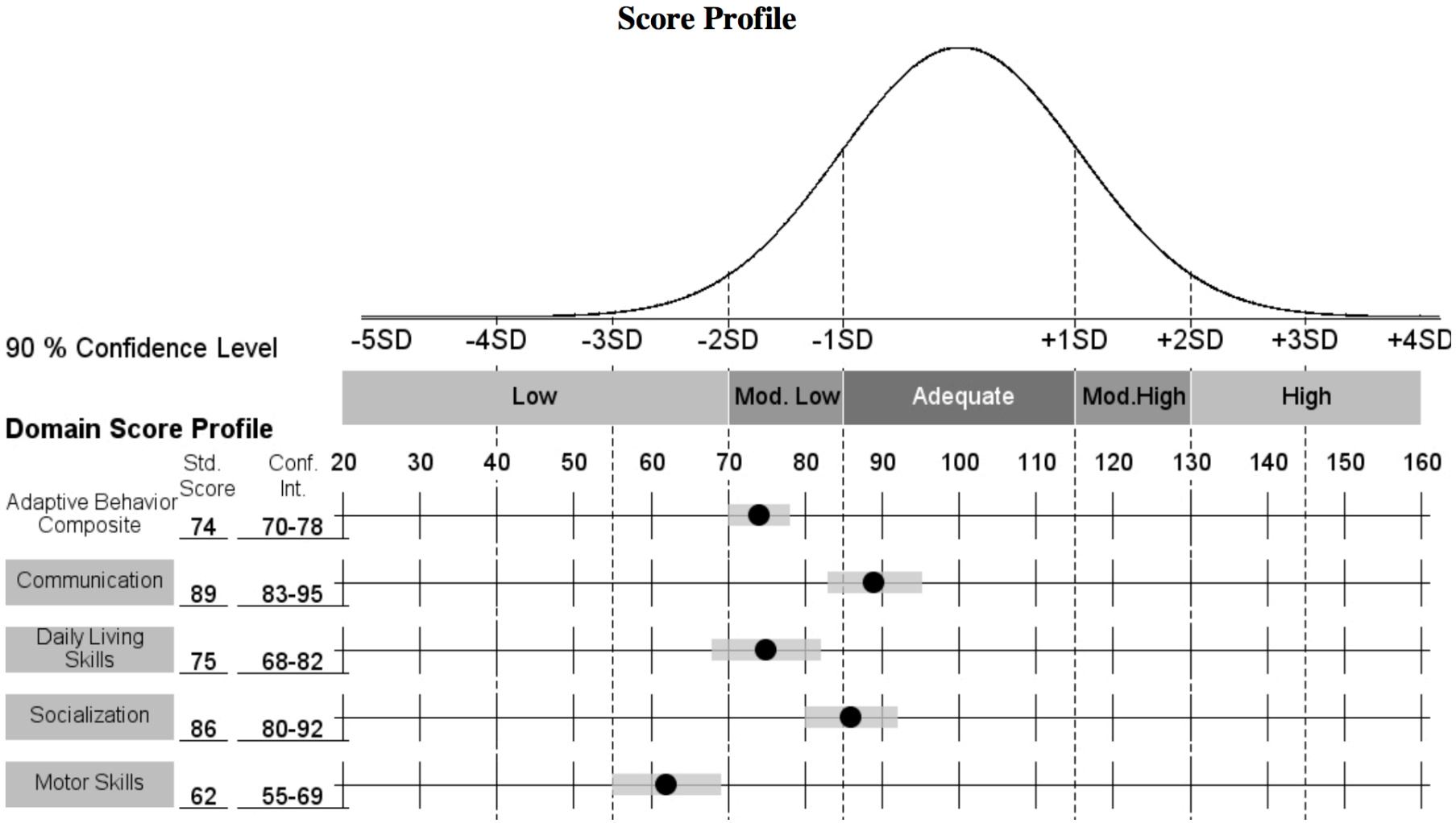
Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

Understanding · Listening and Attending · Following Instructions

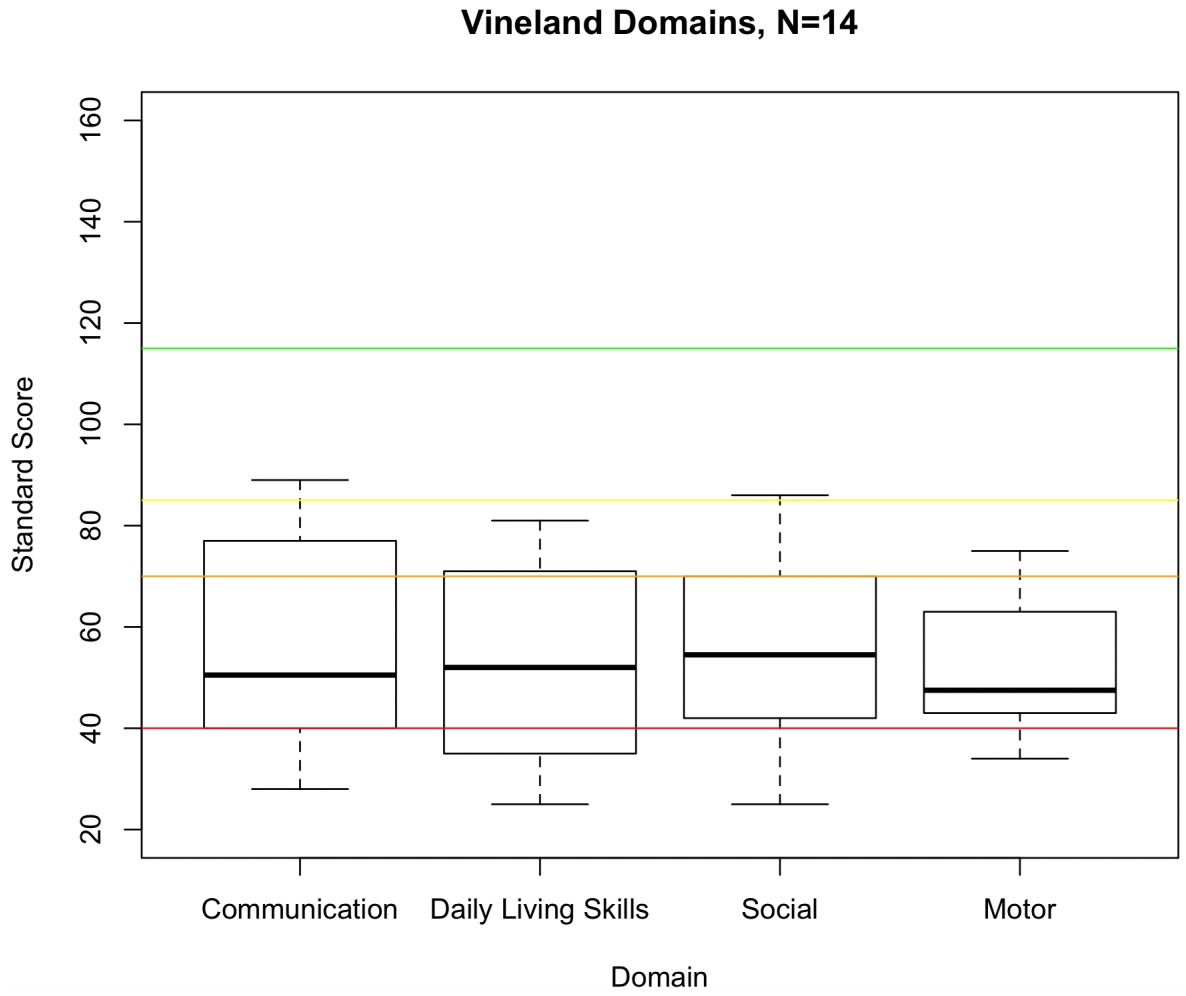
						✔ Check for Comments below
RECEPTIVE	<1 →	1	Turns eyes and head toward sound.		2 1 0 DK	
		2	Looks toward parent or caregiver when hearing parent's or caregiver's voice.		2 1 0 DK	
		3	Responds to his or her name spoken (for example, turns toward speaker, smiles, etc.).		2 1 0 DK	
	1 →	4	Demonstrates understanding of the meaning of *no*, or word or gesture with the same meaning (for example, stops current activity briefly).		2 1 0 DK	
		5	Demonstrates understanding of the meaning of *yes*, or word or gesture with the same meaning (for example, continues activity, smiles, etc.).		2 1 0 DK	
		6	Listens to story for at least 5 minutes (that is, remains relatively still and directs attention to the storyteller or reader).		2 1 0 DK	
	2 →	7	Points to at least three major body parts when asked (for example, nose, mouth, hands, feet, etc.).		2 1 0 DK	
		8	Points to common objects in a book or magazine as they are named (for example, dog, car, cup, key, etc.).		2 1 0 DK	
		9	Listens to instructions.		2 1 0 DK	
		10	Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door"; etc.).		2 1 0 DK	
	3+ →	11	Points to at least five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).		2 1 0 DK	

Scoring based on 4 consecutive '2's and 4 consecutive '0's

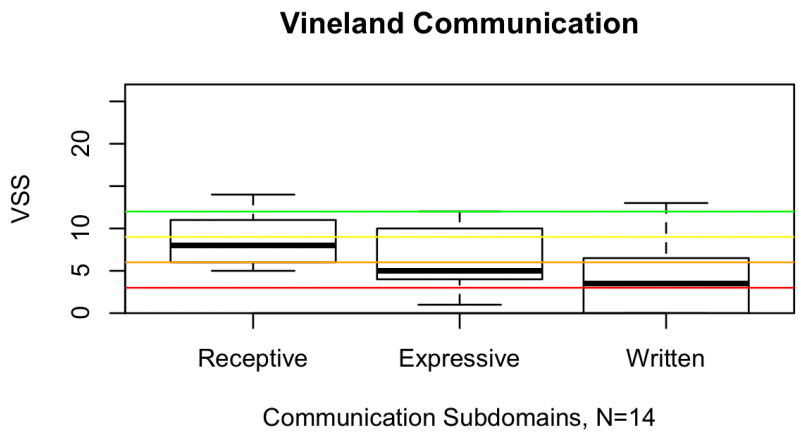
Vineland Adaptive Behavior Scales: Scoring

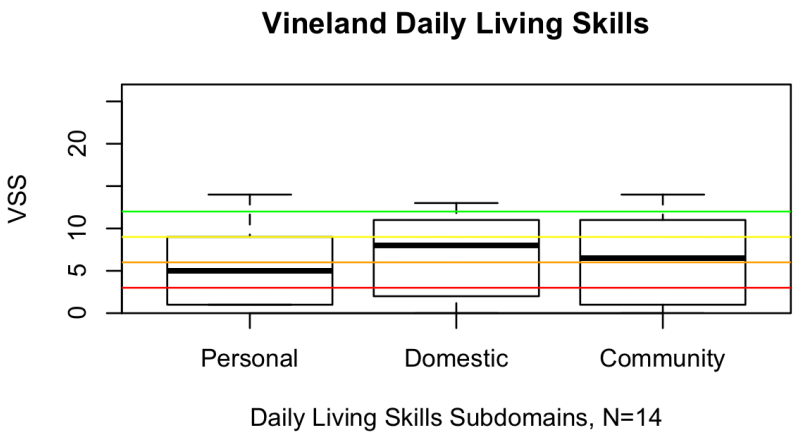


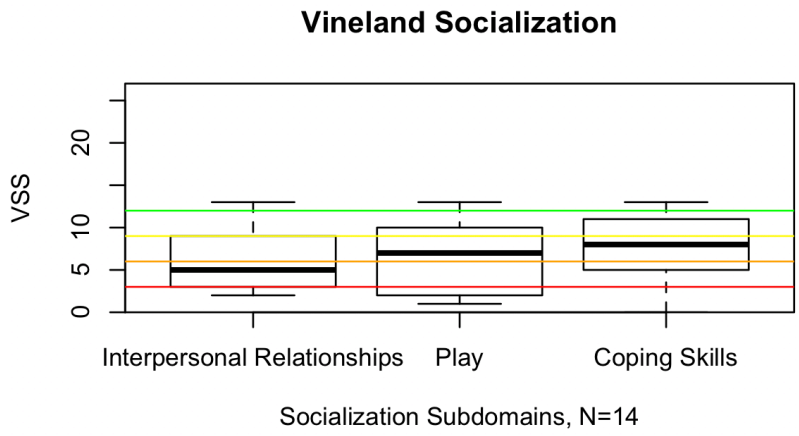
Vineland Domains

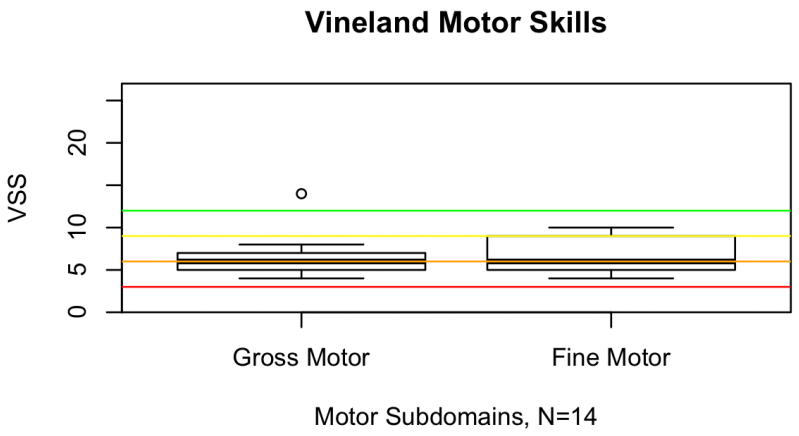


Vineland Subdomains









Next Steps

- Confirm genetic testing results
- Continue recruitment (multiple additional families interested in participating)
- Obtain medical records to get additional details

Questions?

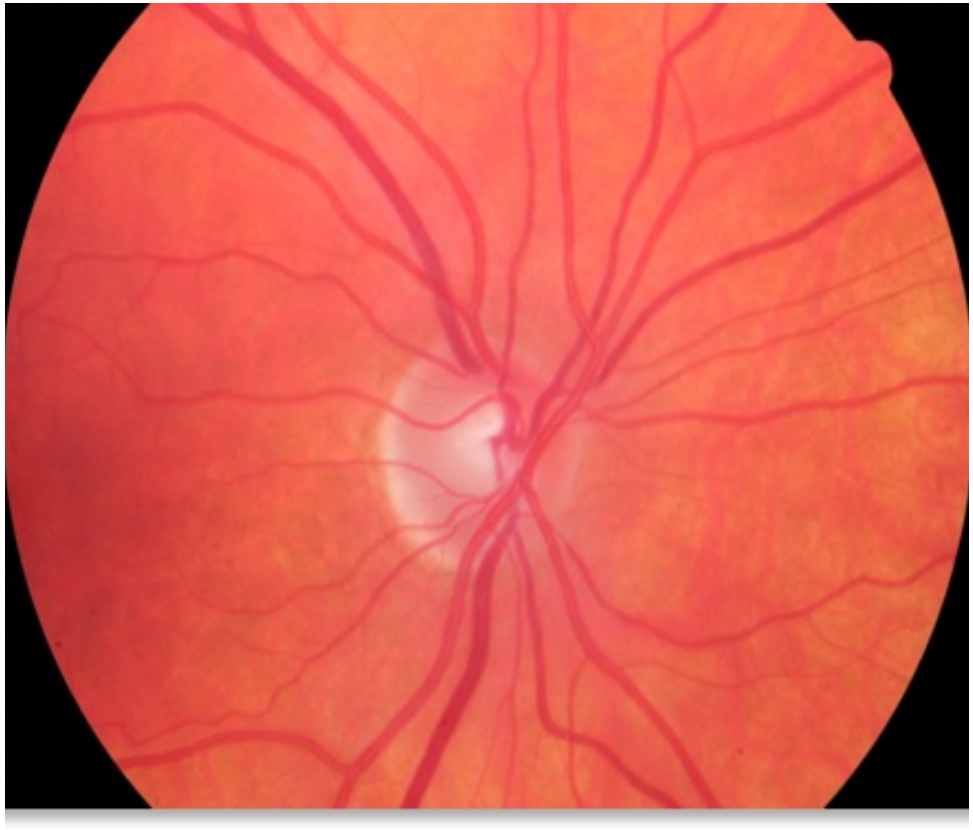
Answering questions about eye issues with *KIF1A*

Steven Brooks, MD

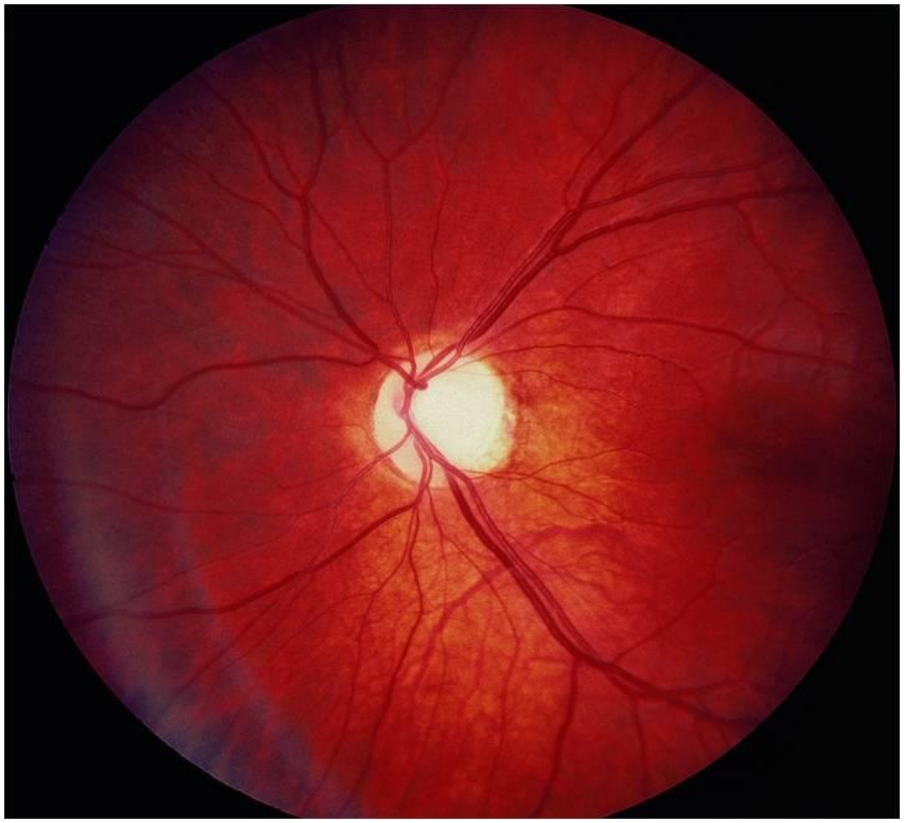
Pediatric Ophthalmologist

Columbia University Medical Center
Department of Ophthalmology

NewYork-Presbyterian
Columbia University Medical Center
Edward S. Harkness Eye Institute



Healthy Optic Nerve



Optic Nerve Atrophy

Supported By
Research to Prevent Blindness

Answering questions about neurological issues with *KIF1A*

Jennifer Bain, MD PhD

Pediatric Neurologist

Morgan Stanley Children's Hospital of NewYork-Presbyterian
Columbia University Medical Center

ColumbiaDoctors | *Child Neurology*

Neurological Assessment in Children with KIF1A

Jennifer Bain, MD, PhD
Assistant Professor

Department of Neurology
Division of Child Neurology

Outline

Who is a pediatric neurologist?

What are the neurological problems associated with KIF1A?

Who is a pediatric neurologist?

Who? *What training do they have?*

- Four years of medical school
- At least 1 to 2 years of pediatric residency
- Three or more years of residency training in adult and child neurology

What? *What diseases do they care for or study?*

Diagnose and treat disorders of the nervous system

- Inclusive of brain, spinal cord, muscles, nerves
- Both acute and chronic care problems

What types of concerns do they evaluate?

Developmental concerns:

- Delays, regression, attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), autism spectrum disorders (ASD), intellectual disabilities

Head problems

- Big heads (macrocephaly) or little heads (microcephaly)

Weird episodes

- Concern for seizures or movement disorders

Febrile seizures or epilepsy

Head complaints

- Concussion, headaches, migraines, brain tumors

Sleep problems

Genetic disorders with known neurological problems

Where? *Where do they practice?*

- Children's hospitals
- University-based medical centers
- Community-based outpatient practices
- Private offices

When*? What ages do they treat?*

- Prenatally, birth and beyond

Why*?*

- Special understanding of medical disorders in childhood
- Special needs of the child and his or her family and environment

A typical neurological consultation:

History (interview and perhaps review of medical records)

Physical examination

Neurological examination

Neurological Exam

Mental status
- Developmental assessment: Speech & language, gross & fine motor, personal & social skills

Cranial nerves = basic functions of the head & neck

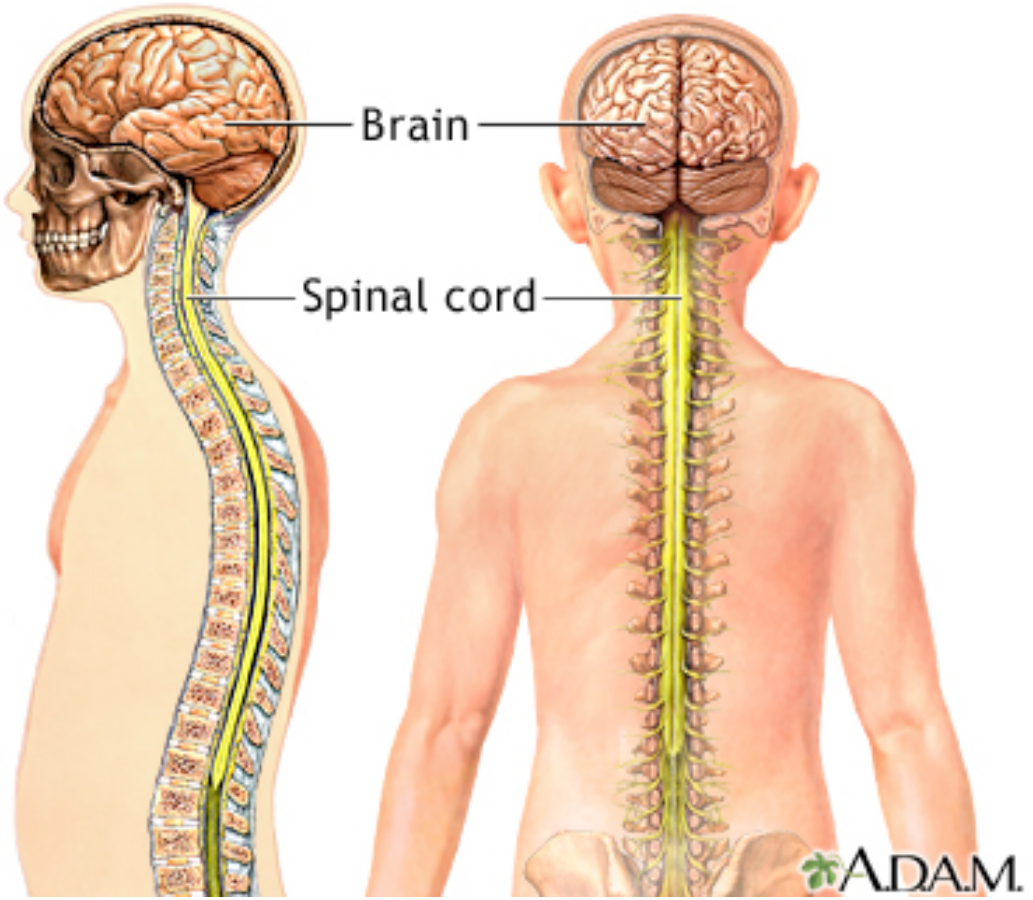
Motor skills

Sensory exam

Reflexes

Coordination

Gait = walking



Neurological Exam

Mental status
- "Who are you?"
- Developmental assessment: Speech & language, gross & fine motor, personal & social skills

Cranial nerves = basic functions of the head & neck

Motor skills

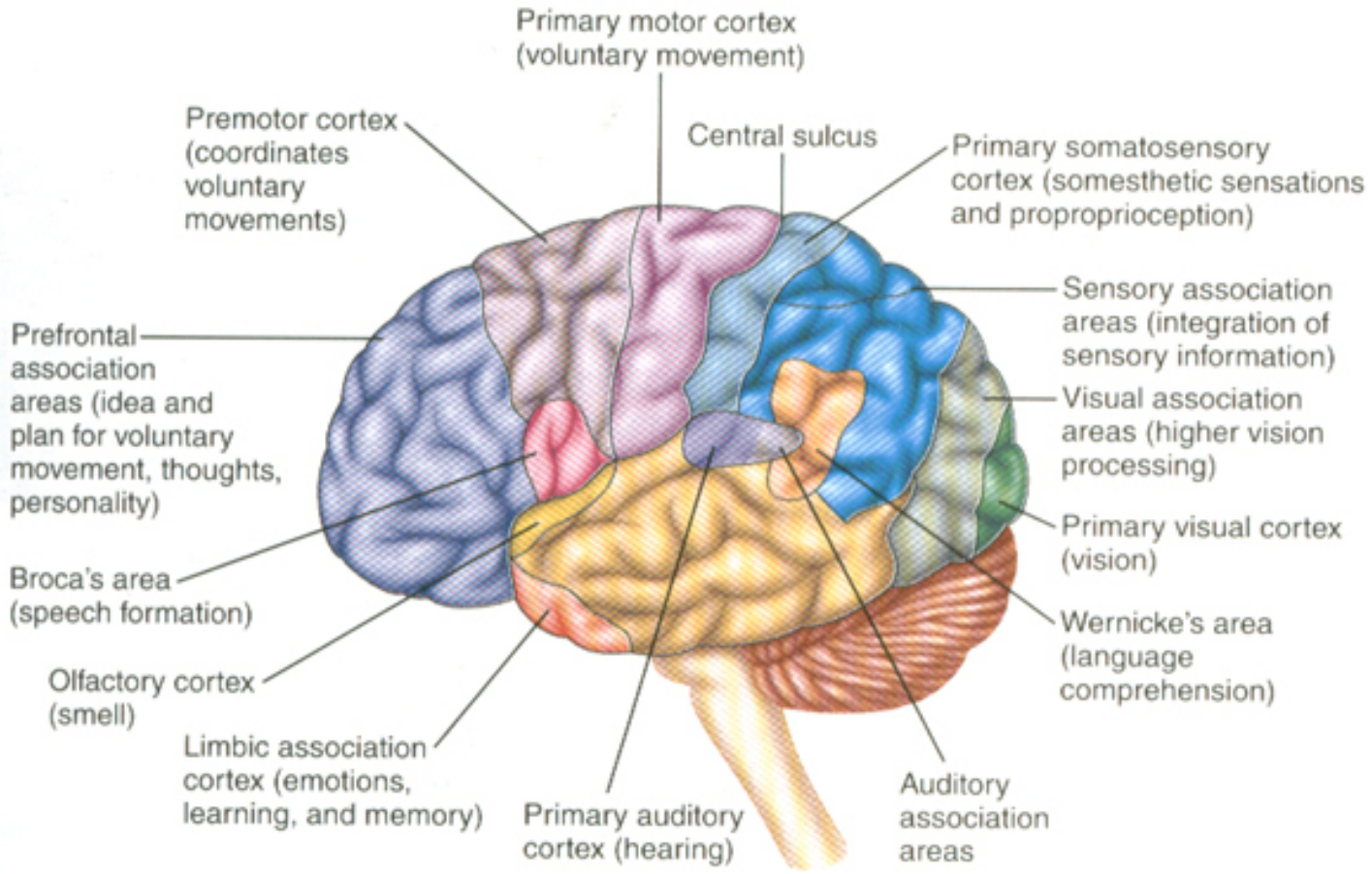
Sensory exam

Reflexes

Coordination

Gait = walking

Functional Organization of the Cerebrum



Developmental Delays → Intellectual Disability

Developmental delays:

- Speech & language
- Gross & fine motor
- Personal & social skills
- Global developmental delay (GDD)

After age 5, the term intellectual disability is used

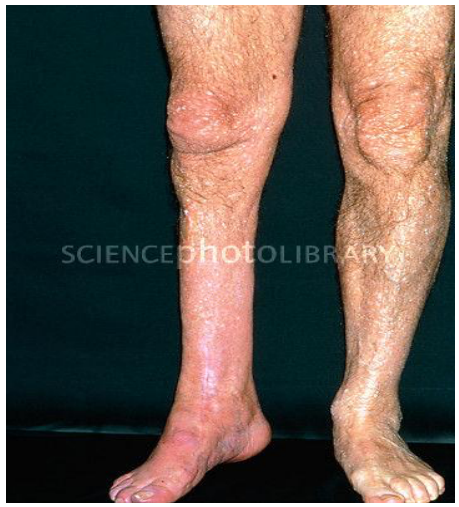
Three criteria must be met:

- **A. Deficits in intellectual functions**
- **B. Deficits in adaptive functioning**
- **C. Onset of intellectual/adaptive deficits during developmental period (<18 yo)**

Motor exam

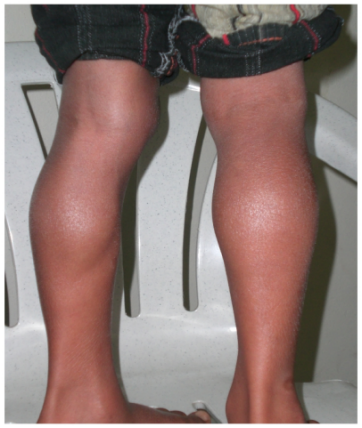
Bulk (how much is there?):

- Too much = Hypertrophy
- Too little? Atrophy



Tone: The resting state of musle

- Too much = Hypertonia
- Too little = hypotonia



Strength: The active state of muscle (how strong are you?)

Weakness, asymmetry when using hands, early hand preference (cerebral palsy)

What mediates tone?

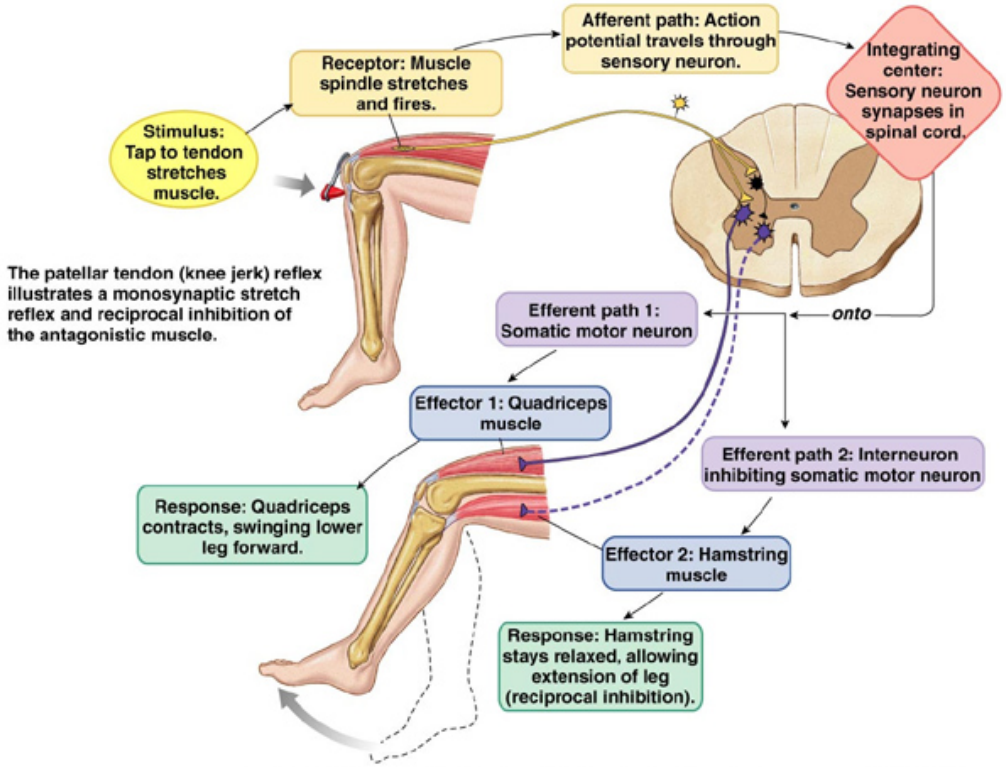
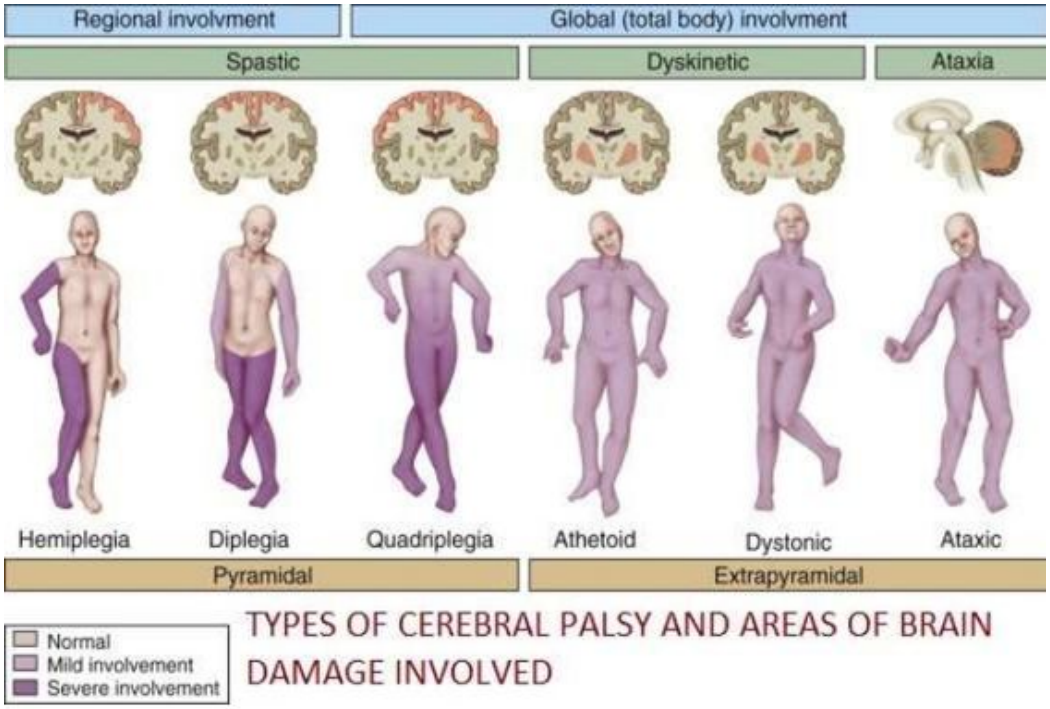


Fig. 13-7

Low tone = Hypotonia

High tone = spasticity or rigidity



TYPES OF CEREBRAL PALSY AND AREAS OF BRAIN DAMAGE INVOLVED

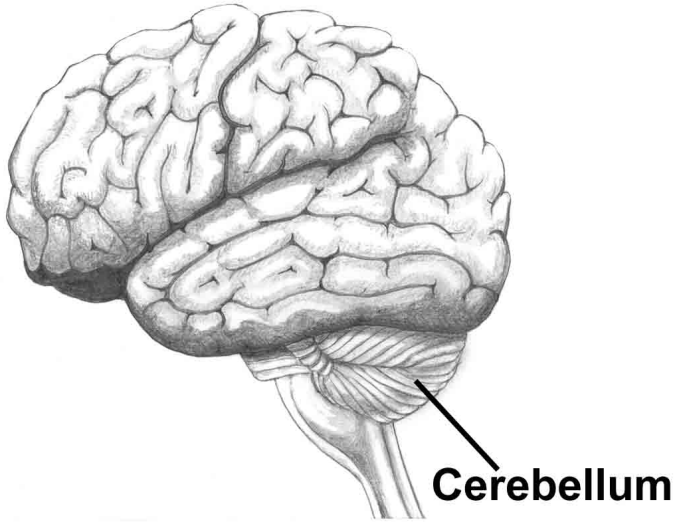
Coordination

Finger to nose = grabbing objects

Dysmetria

Truncal instability =

wobbly when sitting up



Reflexes

- 0/4 = Absent
- 4/4 = Clonus

If ABSENT, think nerve or muscle!

Gait

- Wobbly
- Clumsy
- Wide-based
- Unsteady
- Frequent falls
- Shuffling

If in doubt, ask parents!

Seizures

Electrical activity is caused by complex chemical changes that occur in nerve cells; brain cells either excite or inhibit (stop) other brain cells from sending messages.

Usually there is a balance of cells that excite and those that can stop these messages.

However, when a seizure occurs, there may be too much or too little activity, causing an **imbalance between exciting and stopping activity**. The chemical changes can lead to surges of electrical activity that cause seizures.

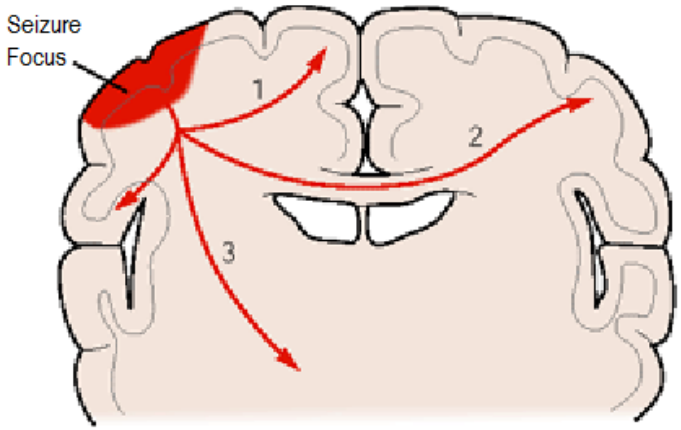
Seizures are not a disease in themselves. Instead, they are a symptom of many different disorders that can affect the brain. Some seizures can hardly be noticed, while others are totally disabling.

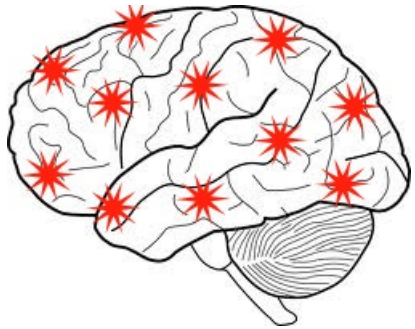
Where do the seizures come from?

Sometimes focal (1 spot)

Sometimes multi focal (more than 2 spot)

Sometimes everything fires off abnormally at that same time (generalized)





How to treat seizures?

Find the underlying cause!

Thank you!

Any questions?

Jennifer Bain jb3634@cumc.columbia.edu

What does *KIF1A* do?

Richard Vallee, PhD

Molecular Geneticist

Open discussion

Gene Therapy & Genome Editing

– Promising individualized medicine

Are we there yet?

- Not quite for most conditions
- Recent developments in research advanced the field

What can families do?

Organize the families: family networking/facebook page

Family meeting

Standardized clinical data collection

- Genetic test reports
- Medical history interview
- Medical record review
- Vineland
- Biorepository

Next steps

Increase the number of identified individuals and confirm the correct diagnosis

- Generalize to other conditions?

Care until the cure

- Understand the natural history and document it well
- Learn practical tips from each other

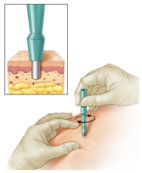
Understand molecular mechanism

Develop reagents to enable researchers and make the reagents widely available

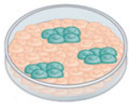
- Cell lines
- Mice

Determine if the condition is reversible and if so when

Learn from other diseases



collect human cells

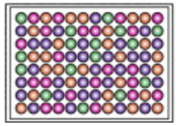


Induced Pluripotential Stem Cells

Neurons

define aberrant protein phosphorylation

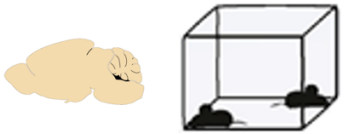
define a cellular phenotype



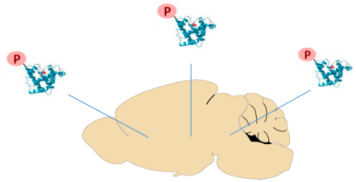
high throughput drug screen

test lead compound in animal models and test for efficacy and toxicity

Create mouse models

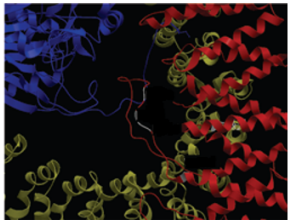


characterize the brain and behavior and how these develop

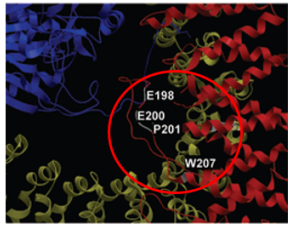


define aberrant protein phosphorylation in different brain regions

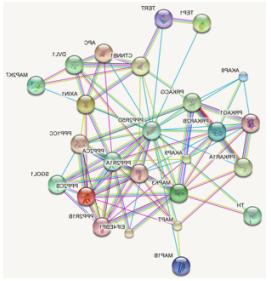
Test for reversibility



3-D protein structure



determine the location of the 4 mutations and the change in protein conformation with the mutations



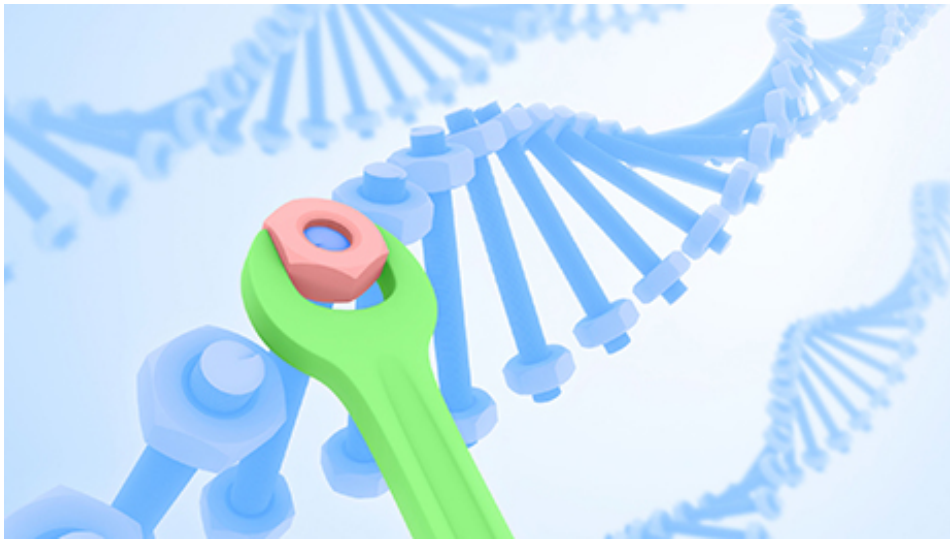
map protein-protein interactions

Gene Therapy & Genome Editing

- Getting there will hopefully take less time
  - Cystic fibrosis (CF) gene was discovered in 1989
  - 1st drug approved in 2012 (23 years later!) – targets 4% of patients with cystic fibrosis
  - 2nd drug approved in 2015 – targets 50%

Gene Therapy

Technique designed to introduce genetic material into cells to compensate for an abnormal gene or to make a beneficial protein



Gene editing

Edit the genetic code making a new generation of medical treatments possible. Can be done precisely but there are challenges.