Clinical Characteristics of CTNNB1

CTNNB1 Connect and Cure Conference

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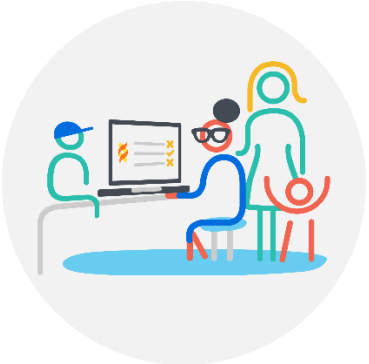
What are the Goals of Simons Searchlight?

Our mission is to shed light on rare genetic neurodevelopmental disorders by collecting high quality, standardized natural history data and building strong partnerships between researchers and families.

Collect detailed medical and behavioral histories along with optional blood samples



Synthesize the information provided and share results back to families

Share deidentified data and samples with qualified researchers

Connect researchers and participants from around the world

Promote better understanding of these genetic variants

Phenotypic Information We Collect

What information is collected from individuals with genetic variants? ‡		Baseline	Annual
Demographic & Genetic	Background History	X	
	Clinical Genetic Lab Results	X	
Medical & Seizures	Medical History, Medication Use	X	X
	Previous Diagnoses (Developmental, Psychiatric)	X	X
	Seizure History	X	X
Sleep	Children's Sleep Habits Questionnaire*	X	
	Simons Searchlight Sleep Supplement	X	
Developmental & Behavioral	Vineland Adaptive Behavior Scales-3*	X	X
	Observer-Reported Communication Ability (ORCA)*	X	X
	Child Behavior Checklists (1.5-5 yr, 6-18 yr)*	X	X
	Adult Behavior Checklist*	X	
	Social Responsiveness Scale-2 (School Age)*	X	X
	Social Communication Questionnaire*	X	
	Quality of Life (Qi-Disability*, PedsQL Family Impact*)	X	
	Brief Developmental Update (Communication, Mobility)	X	X

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‡Includes variants of uncertain significance, likely pathogenic, and pathogenic variants

**Publisher measure*

CTNNB1 Publications with Simons Searchlight

Recruited CTNNB1 Simons Searchlight Participants

- Diagnostic preferences include discussion of etiology for adults with cerebral palsy and their caregivers (Aravamuthan et al., Dev Med Child Neurol., 2022)

Analyzed Simons Searchlight data and biospecimens submitted by CTNNB1 families

- Clinical phenotypic spectrum of CTNNB1 neurodevelopmental disorder (Sudnawa et al., Clin Genet., 2024)
- Motor phenotypes associated with genetic neurodevelopmental disorders (Almansa et al., Ann Clin Transl Neurol., 2024)
- Clinical and neuropsychological phenotyping of individuals with somatic variants in neurodevelopmental disorders (Mo and Walsh, Neurol Genet., 2025)
- Comparison of autism domains across thirty rare variant genotypes (Ali et al., eBioMedicine., 2025)

Highlighted research collaboration of CTNNB1 Connect and Cure and Simons Searchlight

- Paving the way toward treatment solutions for CTNNB1 syndrome: a patient organization perspective (Miroševič, Khandelwal et al., Ther Adv Rare Dis, 2025)

The CTNNB1 Registry in Simons Searchlight

Progress of Individuals with CTNNB1

STEP 1
Sign up online.

296

STEP 2
Provide your genetic lab report.

238

STEP 3
Share your important medical history.

157

STEP 4
Fill out surveys.

191

STEP 5
Provide a blood sample if you are interested.

55

STEP 6
Update us every year.

Login for more

We are a long-term study, gathering new information from you every year.

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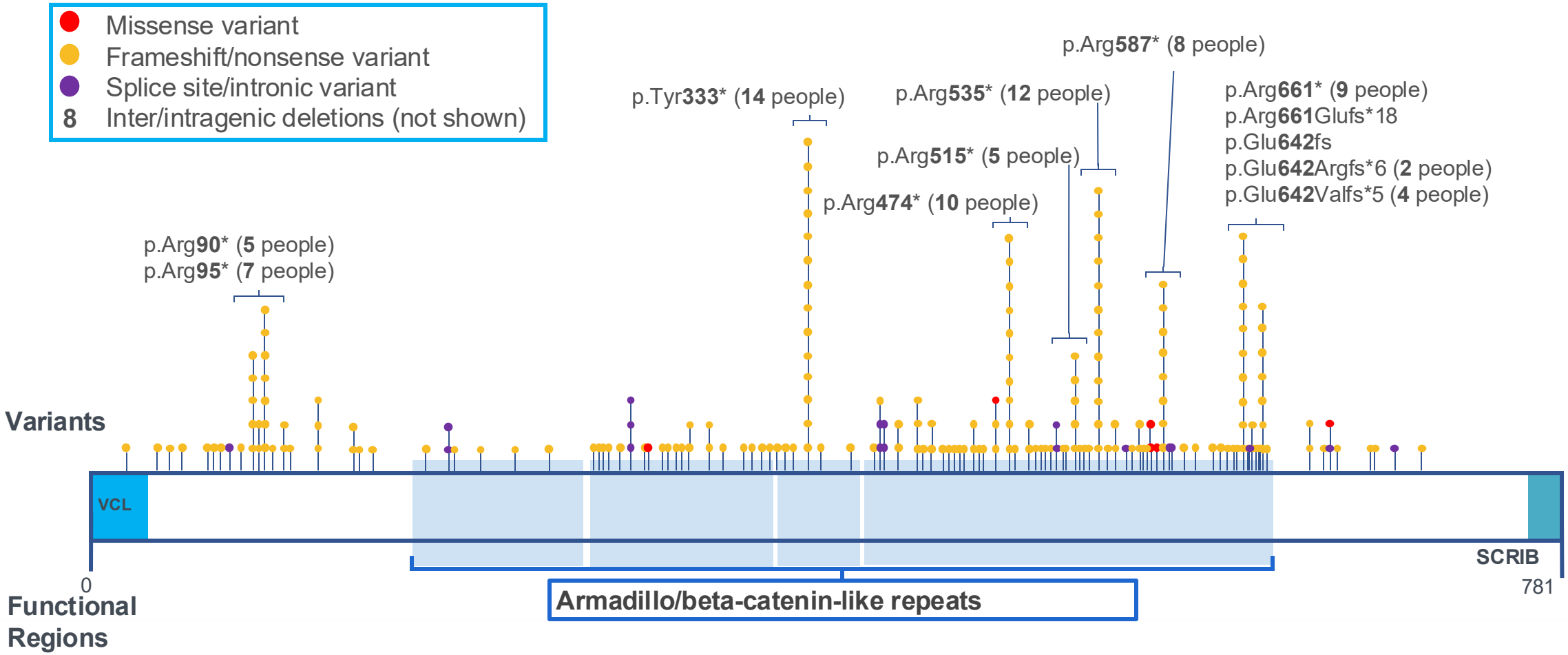
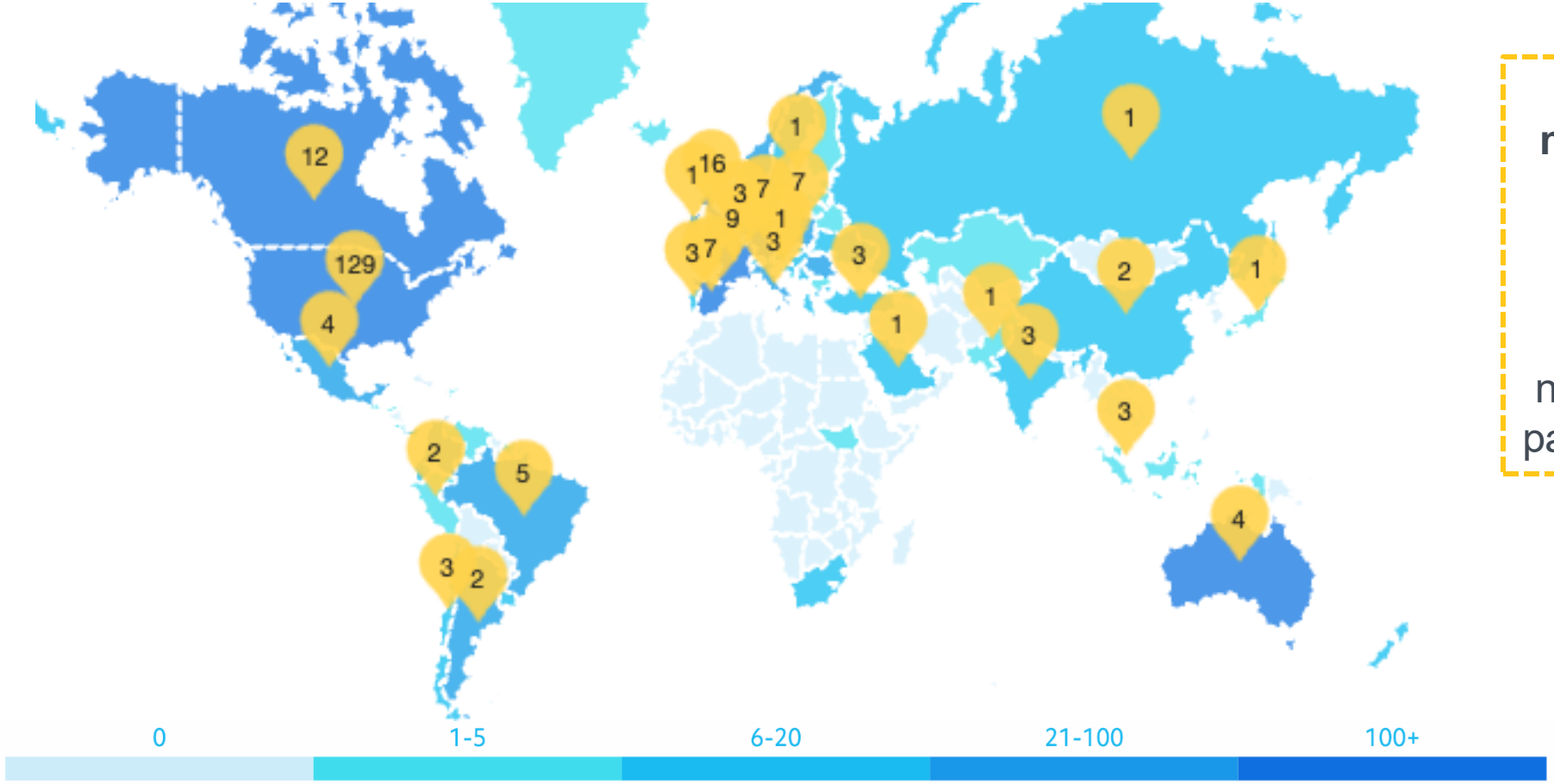
Counts include participants with variants of uncertain significance, likely pathogenic, and pathogenic variants.

CTNNB1 Pathogenic and Likely Pathogenic Variants (225 participants, 74 more than the last meeting)



11 Simons Searchlight VUS participants not shown

Simons Searchlight families live in **83** countries globally, including **235 CTNNB1** participants in **28** countries.



Darker color = **more** participants in country (all gene groups)

Map markers = number of **CTNNB1** participants in country

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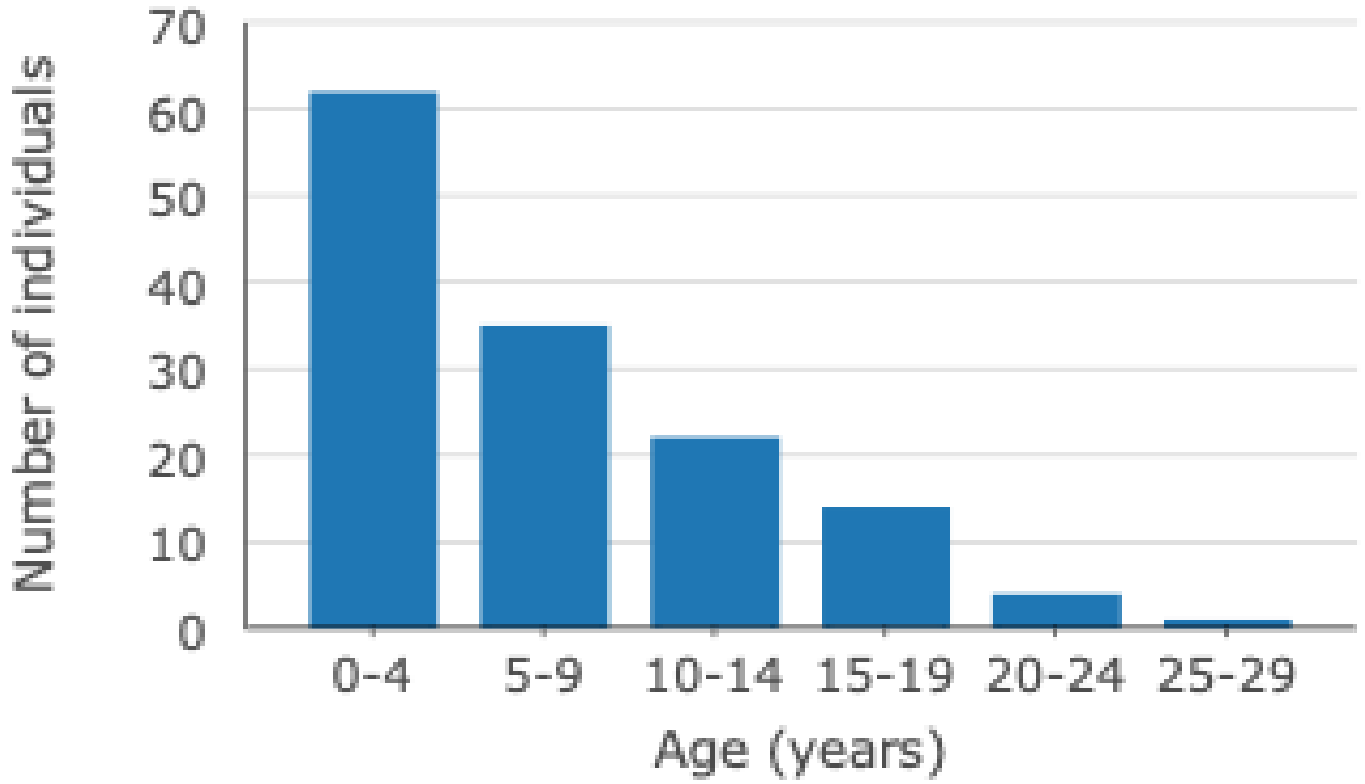
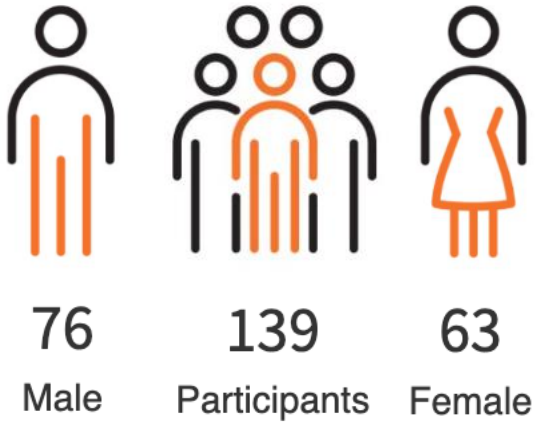
Simons Searchlight CTNNB1 Medical History Data

*Includes survey data from individuals with likely pathogenic and pathogenic variants

Age at Most Recent Medical History Interview
(139 individuals)



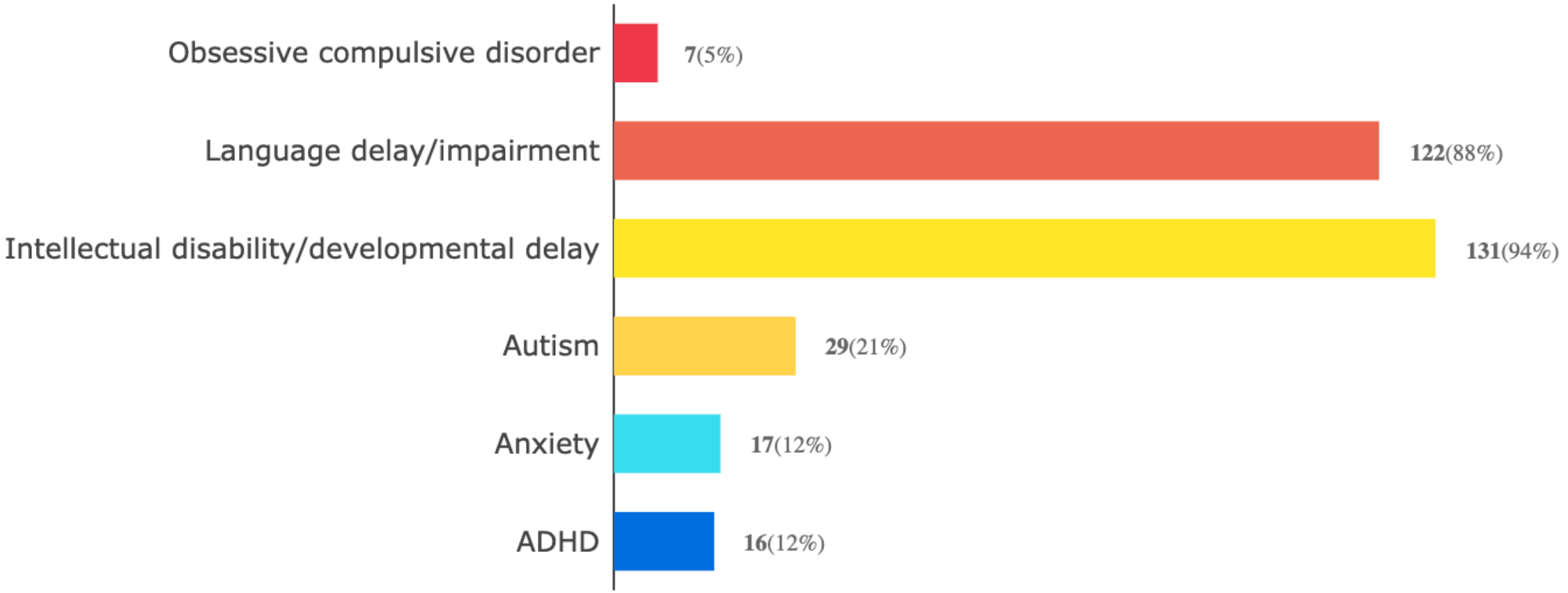


Age Range
6mo(s) - 26yr(s)

131
Participants under 18

Average Age
7 yr(s)

Developmental and Behavioral Conditions
(139 individuals)

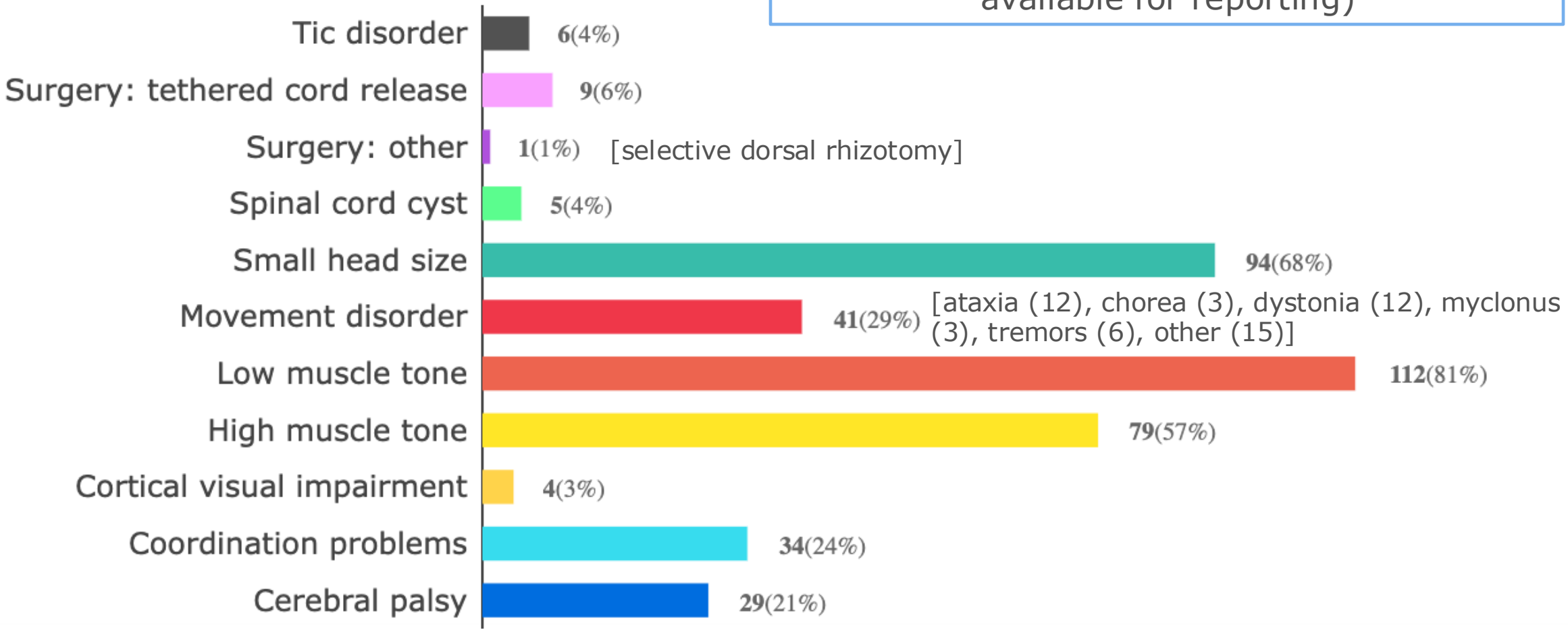


Medical Issues Overview
(139 individuals)

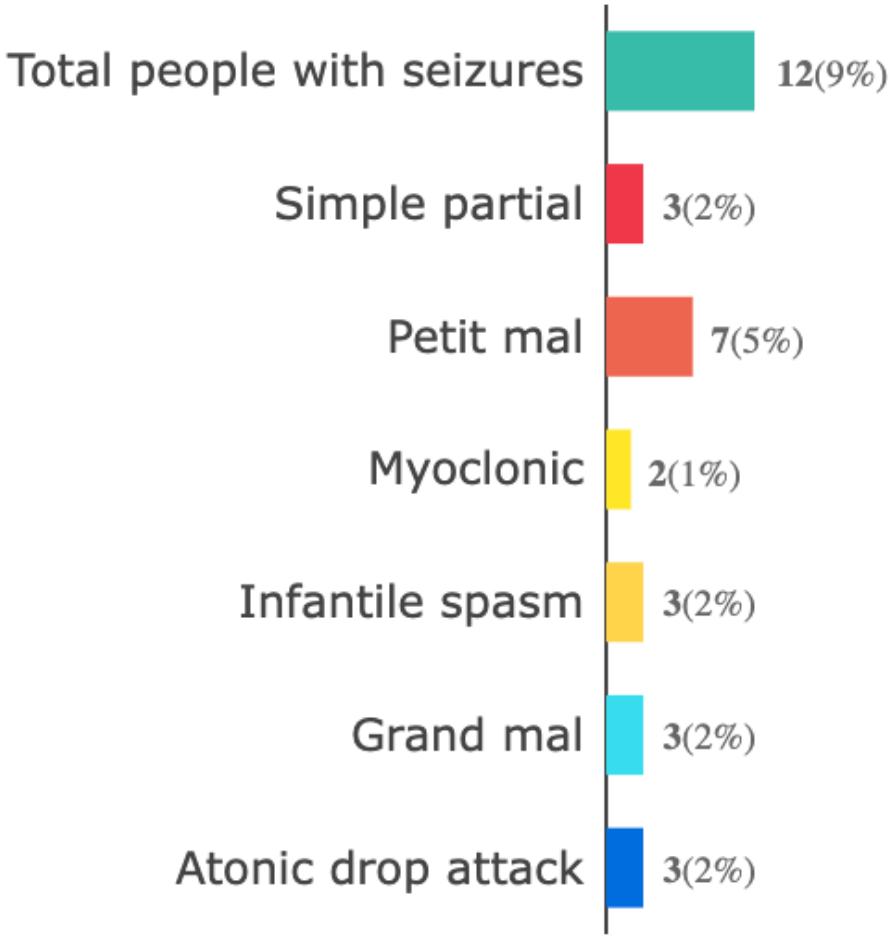
*conditions listed in brackets represent a non-exhaustive list of the most common conditions within the specific bar graph category

Tethered cord newly added to medical history neurological condition list (data not yet available for reporting)

Neurological
(139 individuals)



Seizures
(139 individuals)



Seizure Course

Available in **17 individuals with seizures** completing the Seizure History Survey*

- Seizure onset was from 2 months through 8 years
  - Average age of first seizure is 3.6 years
- **12 (71%)** of individuals with seizures have had to take medication for their seizures
  - **9 (75%)** continue to take preventative medication for their seizures
- **8 (47%)** of all individuals who ever had a seizure have achieved seizure control or remission
  - Average age at seizure control was 5.8 years, ranging from 9 months to 17 years

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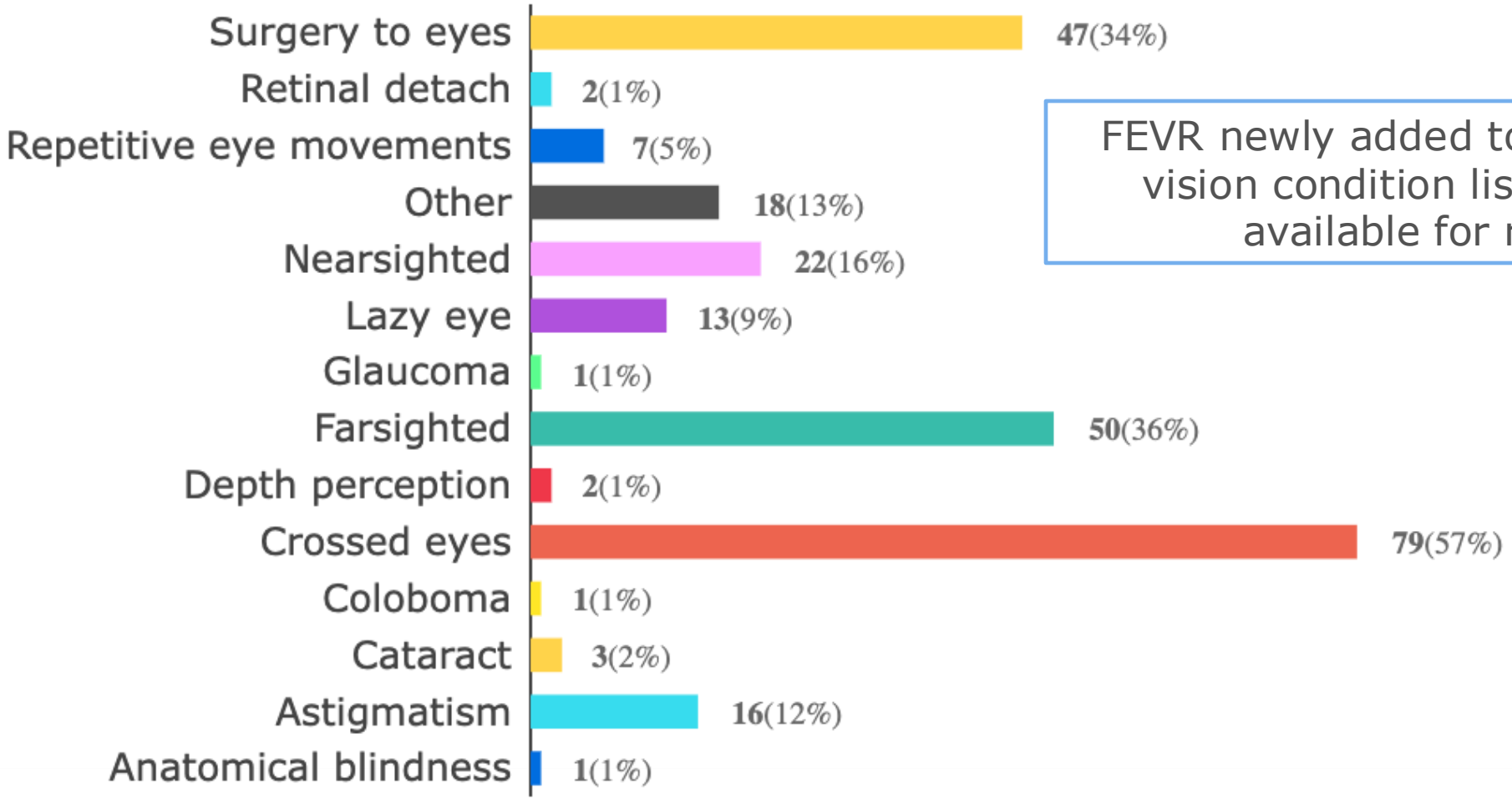
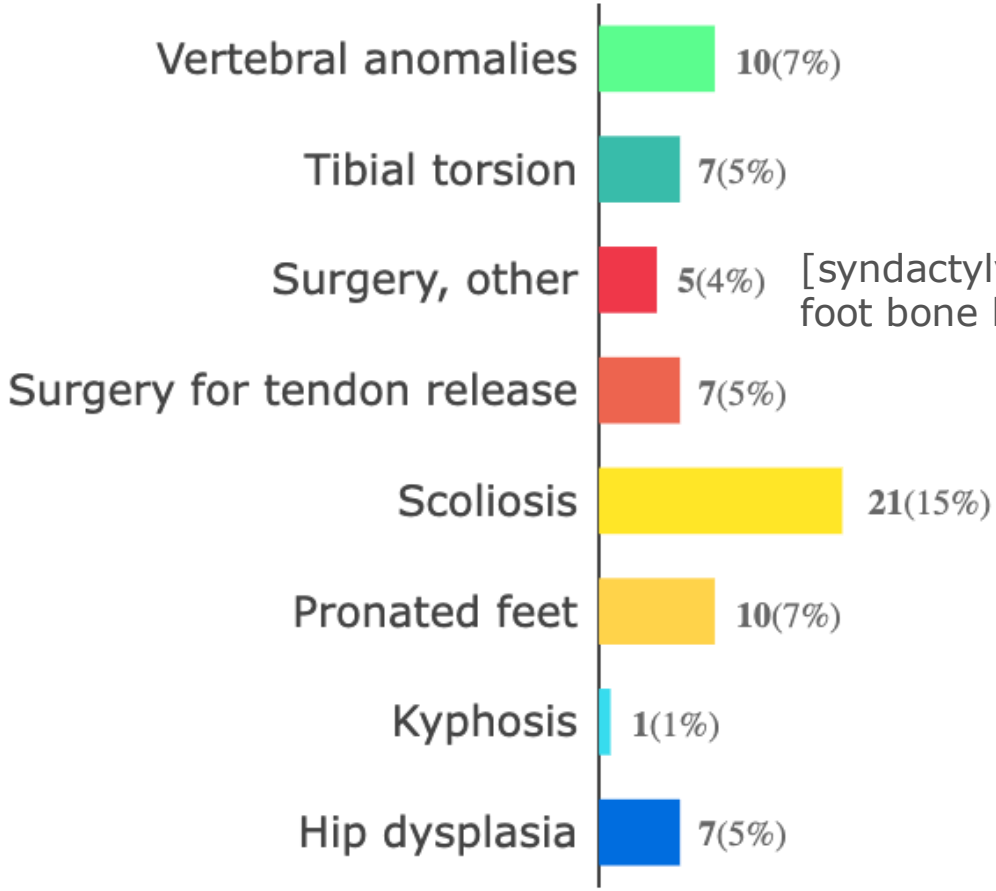
*Number of people with seizures may differ from previous slide, sourced from a different survey

Vision
(139 individuals)



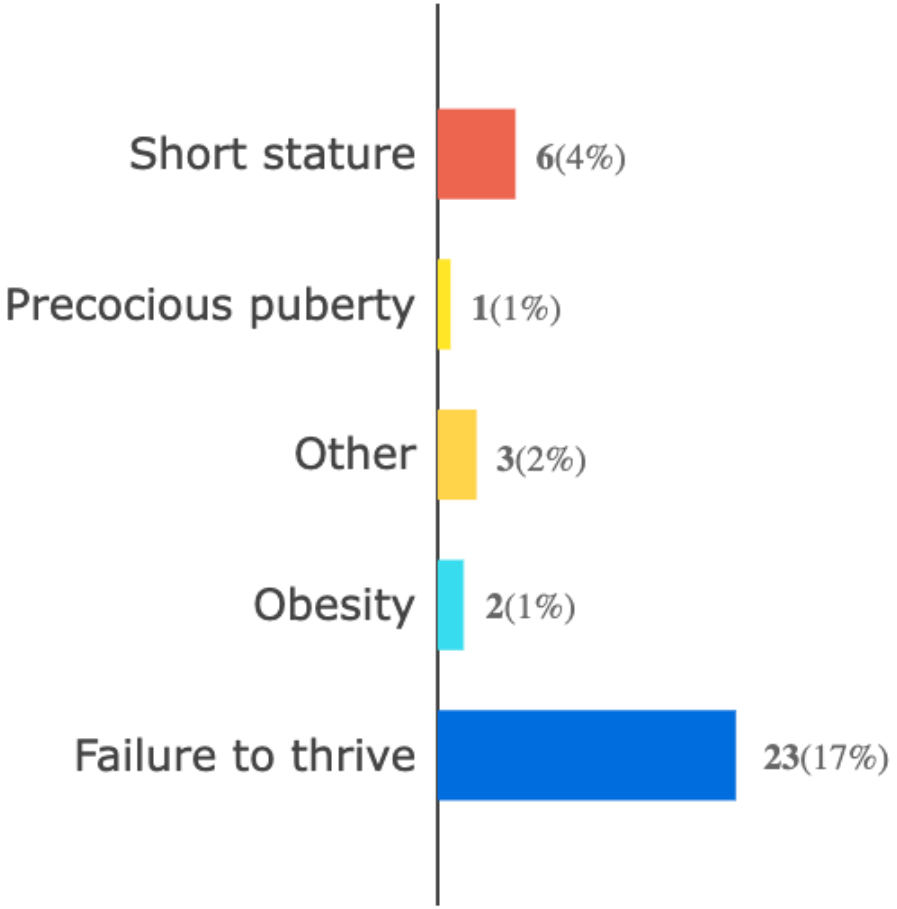
FEVR newly added to medical history vision condition list (data not yet available for reporting)

Orthopedic
(139 individuals)

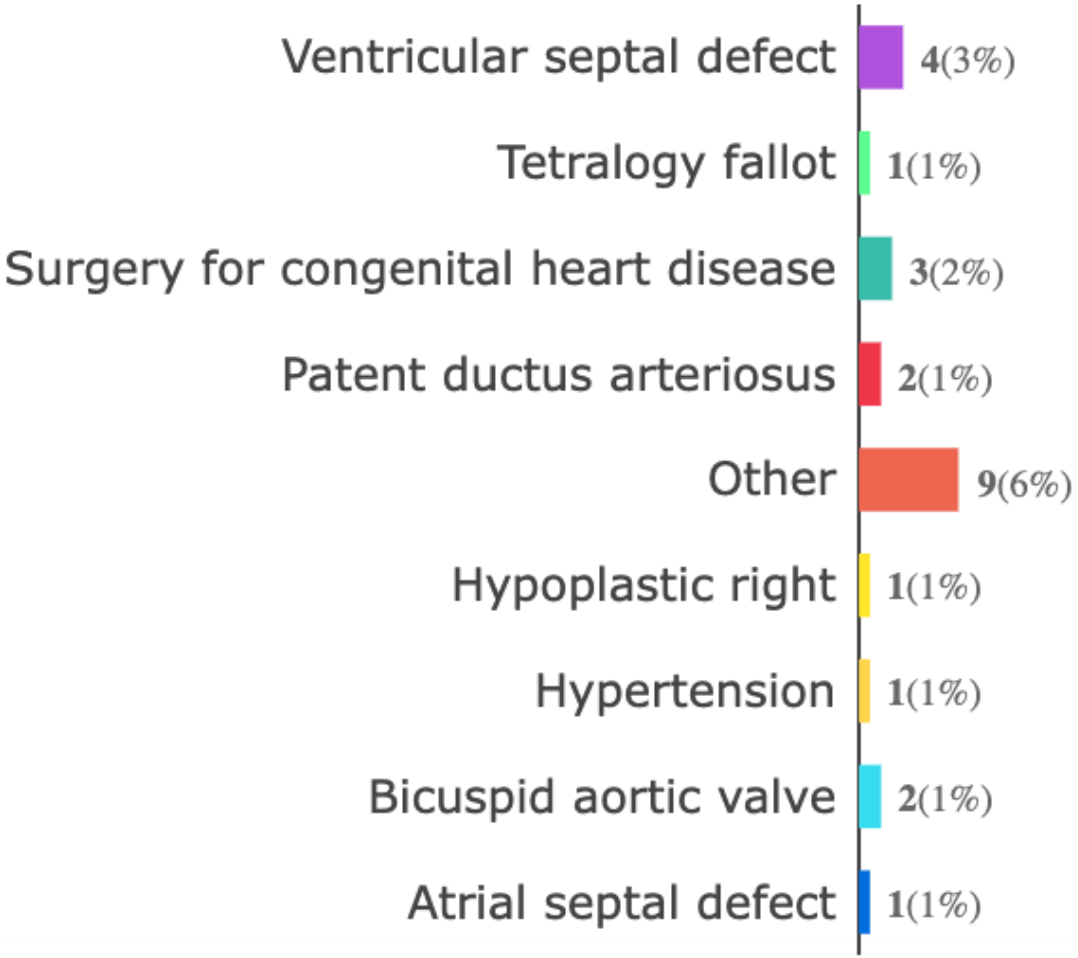


[syndactyly/polydactyly surgery (1), spinal fusion (1), laminectomy (1), foot bone lengthening (1), unspecified (1)]

Endocrinologic
(139 individuals)

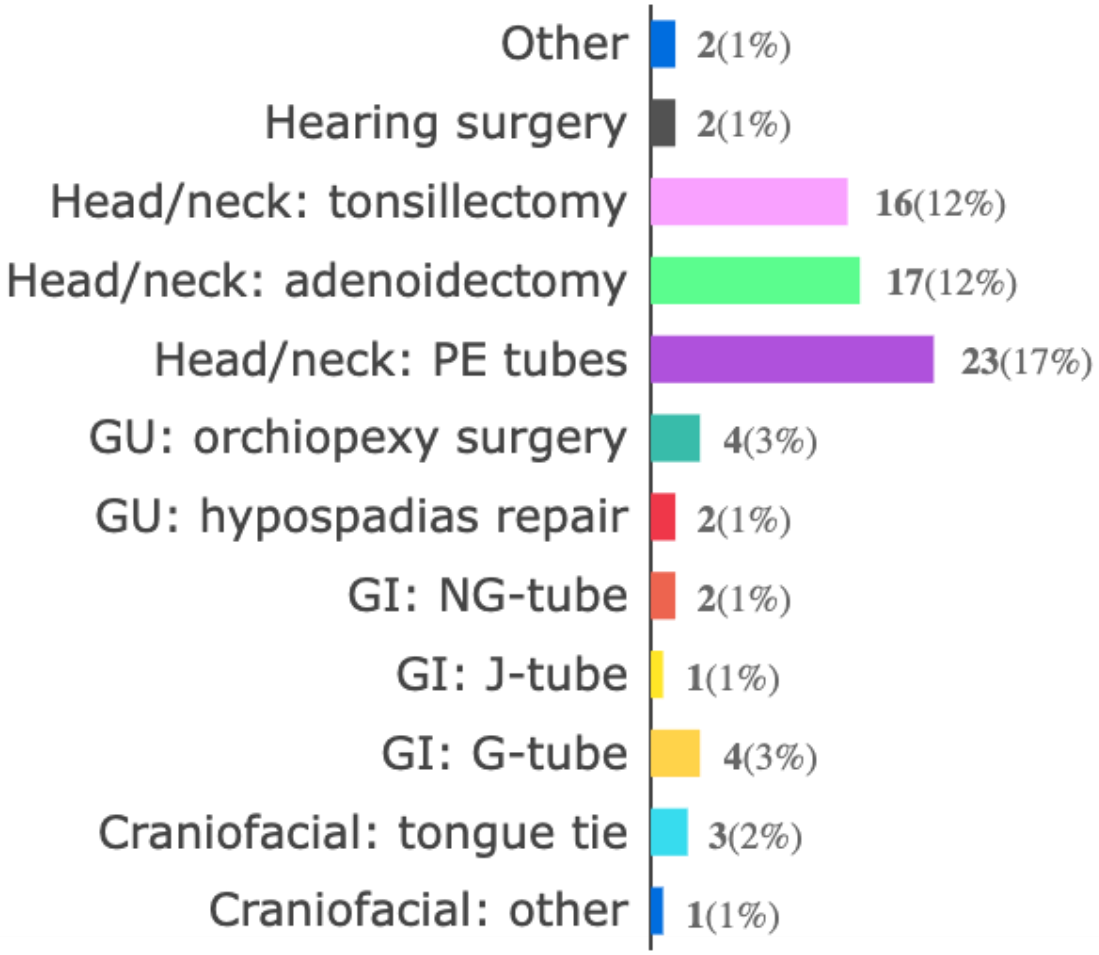


Heart
(139 individuals)

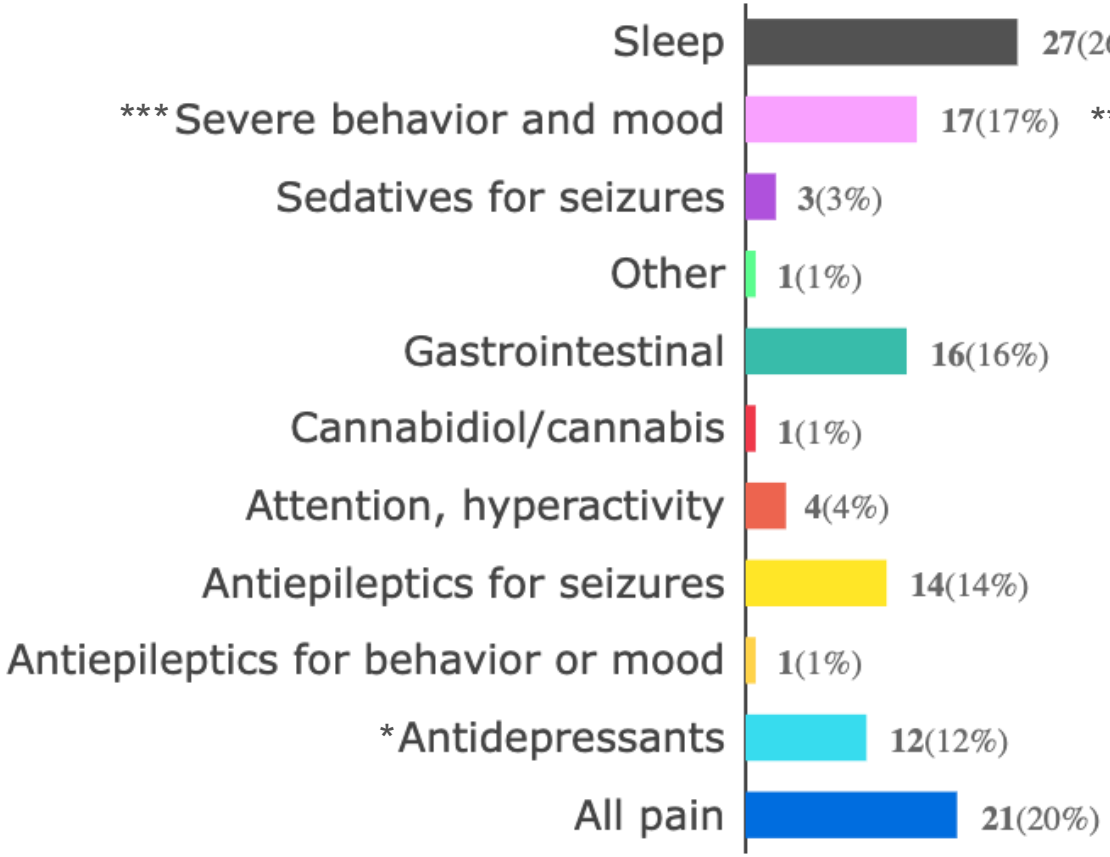


Additional Surgeries Not Yet Shown

(139 individuals)



Medication Use
(103 individuals)



****Neuroleptics and mood stabilizers, including for sleep*

**Antidepressants are also used for anxiety, OCD, and other mood or behavior*

Most Effective Seizure Medications Reported
(18 individuals)

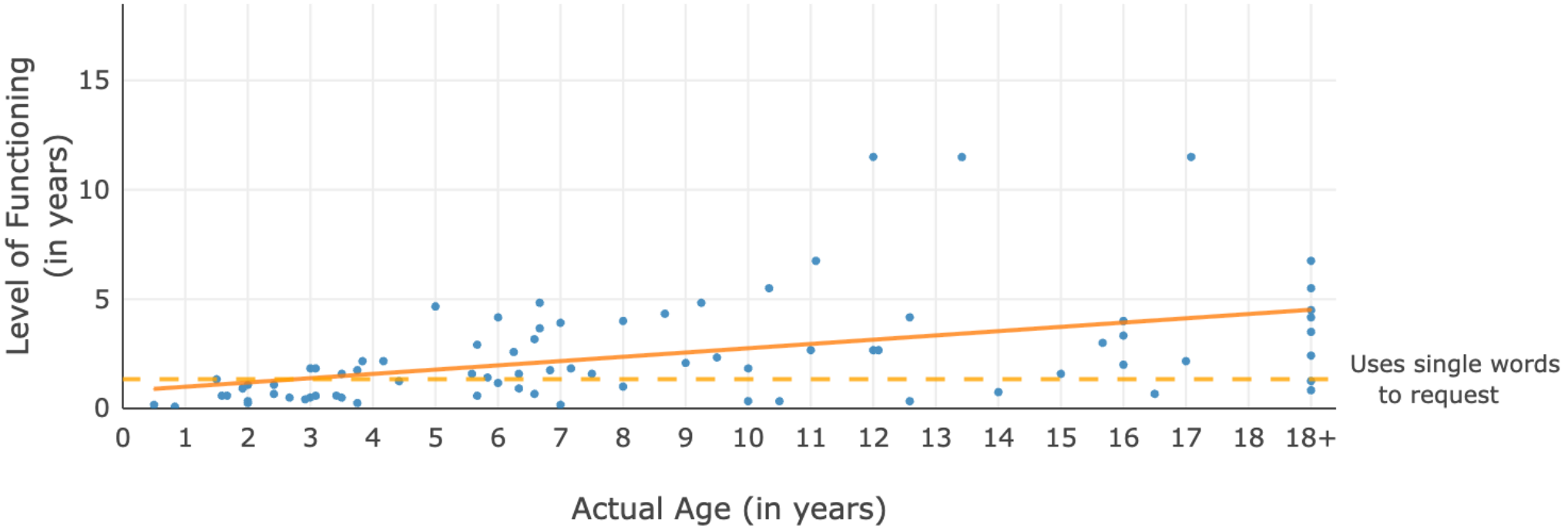
We asked caregivers if there was a medication that seemed to work best for their dependent's seizures

Levetiracetam stood out as most effective, though no one medication necessarily works for all individuals.

Vineland Adaptive Behavior Scales (Vineland-3)

*Includes survey data from individuals with likely pathogenic and pathogenic variants

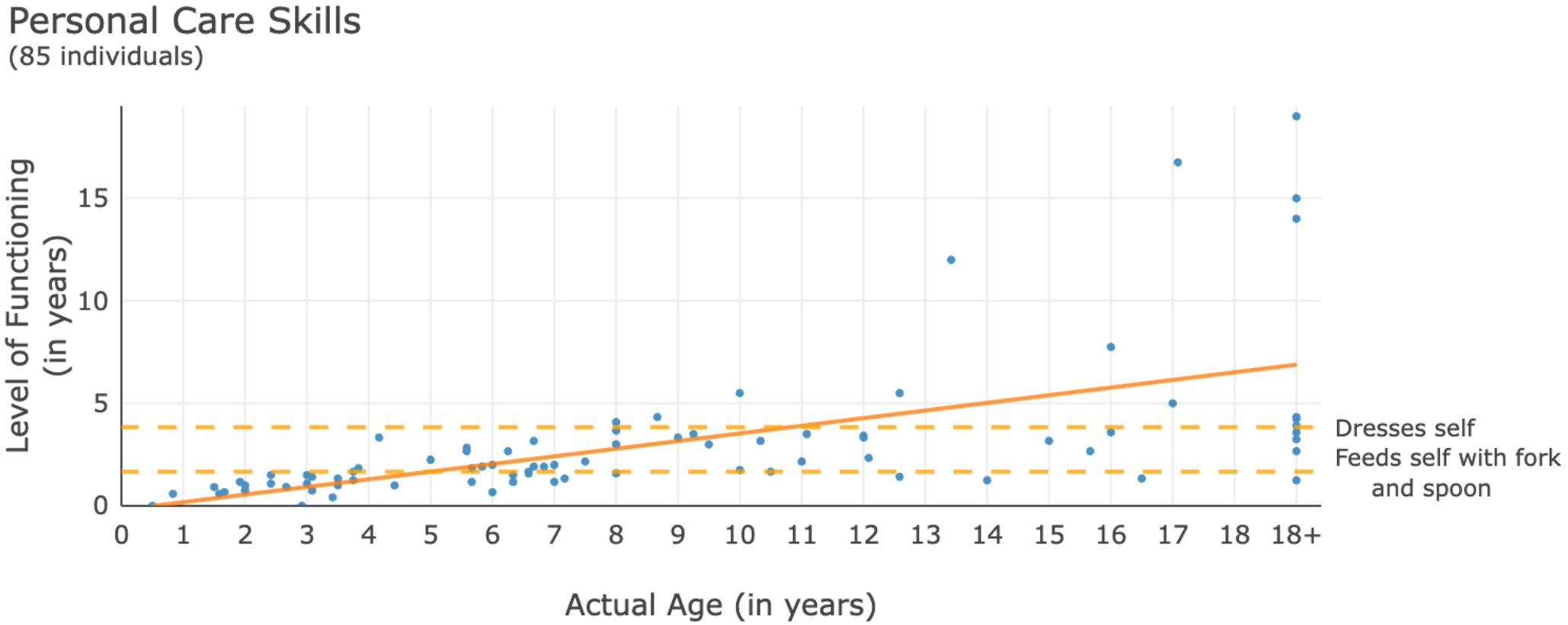
Expressive Language Development
(82 individuals)



3 excluded as potential outliers (level of functioning in years greater than actual age in years)

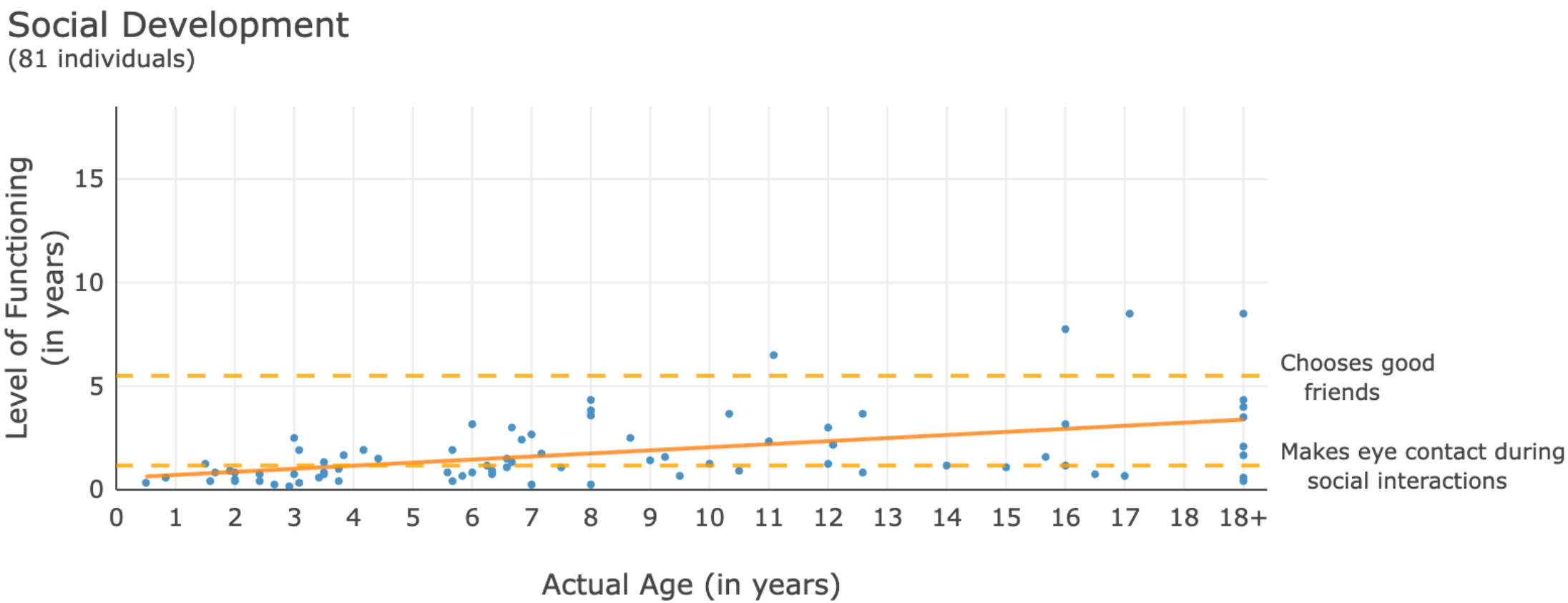
What does this mean as my child gets older?

Along the bottom is the actual age of the person.	The dots are placed at the *level* at which they express themselves.	**76%** of individuals are likely to be using language at age 4 and older.



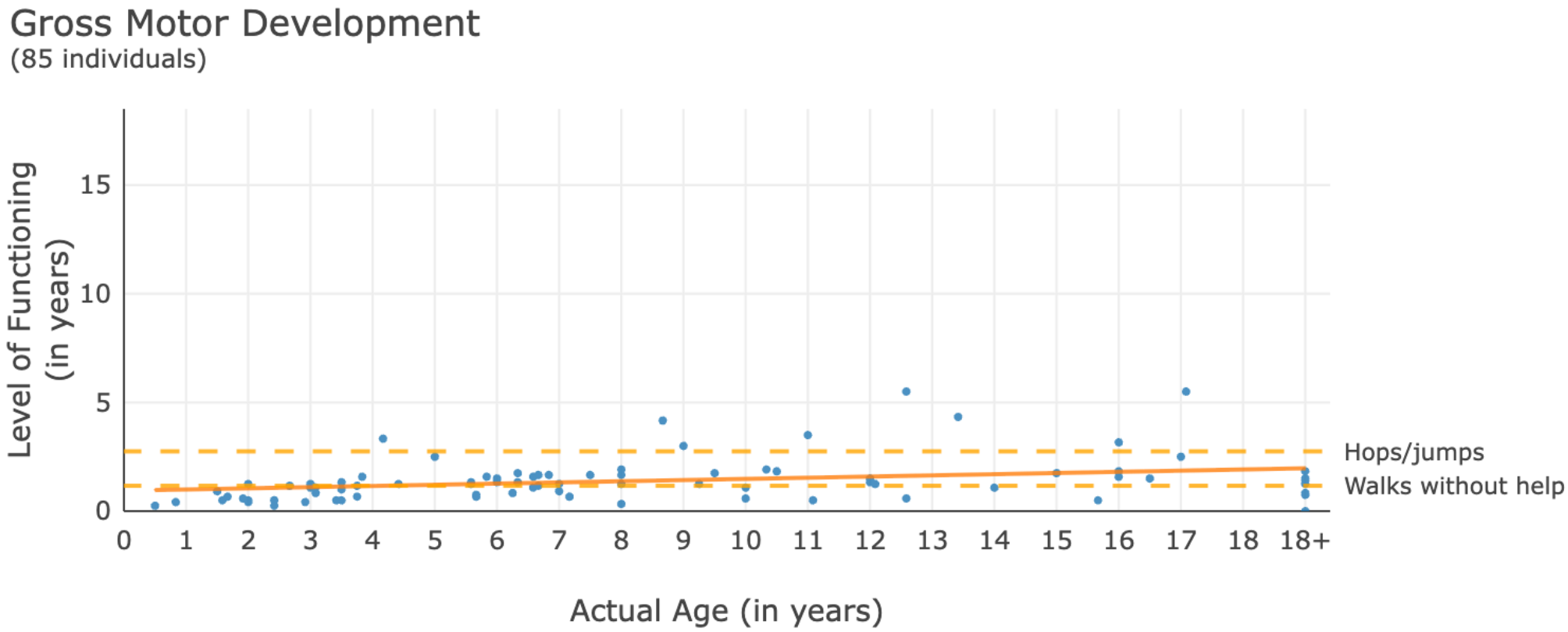
What does this mean as my child gets older?

Along the bottom is the actual age of the person.	The dots are placed at the *level* at which they can do things for themselves.	**79%** of individuals are likely to be feeding themselves at age 4 and older.



4 excluded as potential outliers (level of functioning in years greater than actual age in years)

What does this mean as my child gets older?	Along the bottom is the actual age of the person.	The dots are placed at the *level* of their social behaviors.	**68%** of individuals are likely to make eye contact at age 4 and older.



What does this mean as my child gets older?

Along the bottom is the actual age of the person.	The dots are placed at their *level* of motor skills like walking.	**72%** of individuals are likely to be walking at age 4 and older.

Child Behavior Checklist (CBCL)

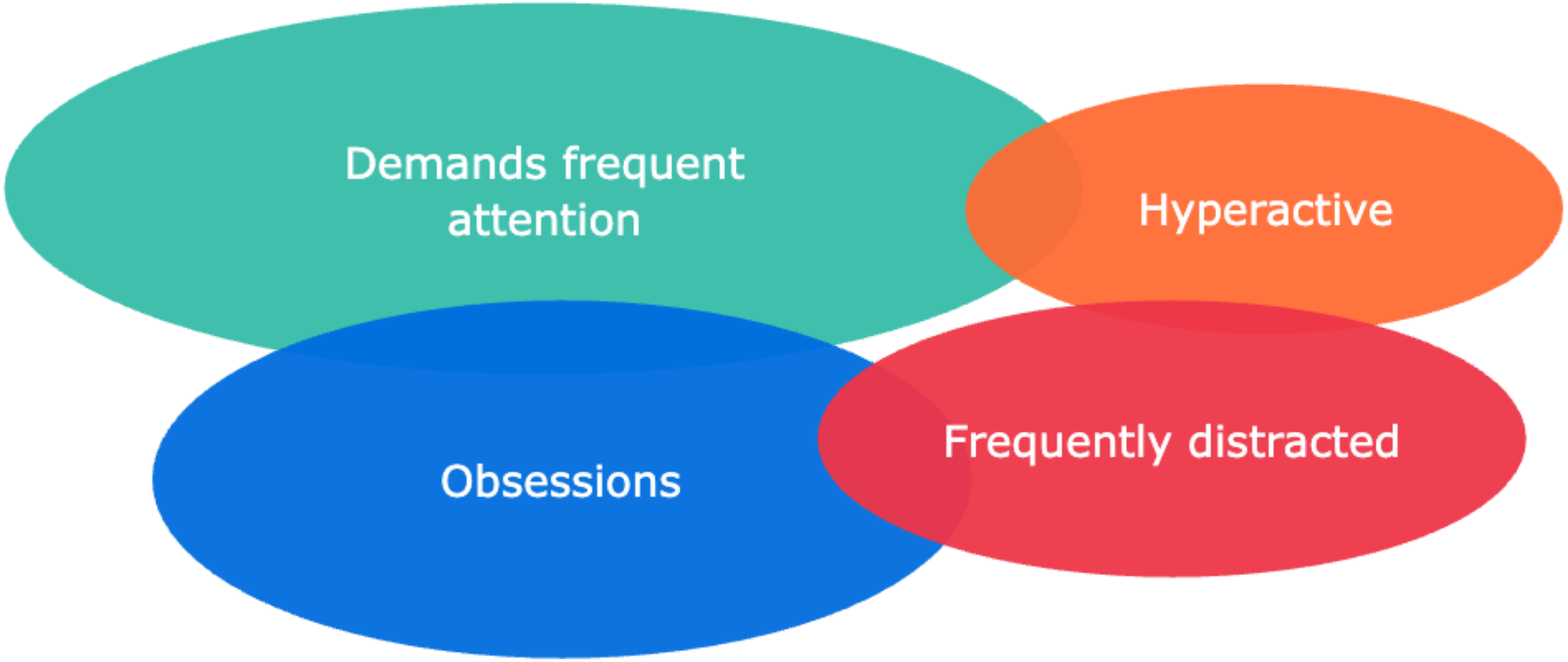
*Includes survey data from individuals with likely pathogenic and pathogenic variants

Top Behavioral and Emotional Concerns

Ages 1.5-5 Years (33 individuals)

Top Behavioral and Emotional Concerns

Ages 6-18 Years (55 individuals)



CTNNB1 Neurodevelopmental Disorder

32 individuals with likely pathogenic or pathogenic *CTNNB1* variants

Common Neurological Symptoms

- Truncal hypotonia
- Muscle weakness
- Hypertonia
- Dystonia
- Microcephaly
- Tethered cord

Cognitive and Adaptive Function

- Mean DAS-II general conceptual ability composite score = 58.3
- Mean Vineland adaptive behavior composite standard score = 66.5

Motor Difficulties

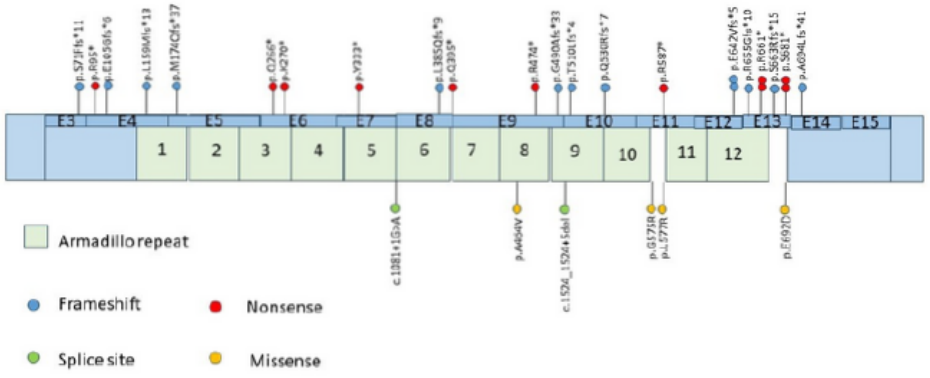
- Non-ambulatory 25%
- Mean GMFM-66 score = 56.6

Common Behavioral Issues

- Autism
- ADHD
- Sleep problems

Common Ophthalmologic Symptoms

- Strabismus
- Hyperopia
- Familial exudative vitreoretinopathy



Quality of Life

- Mean overall quality of life score = 81.7

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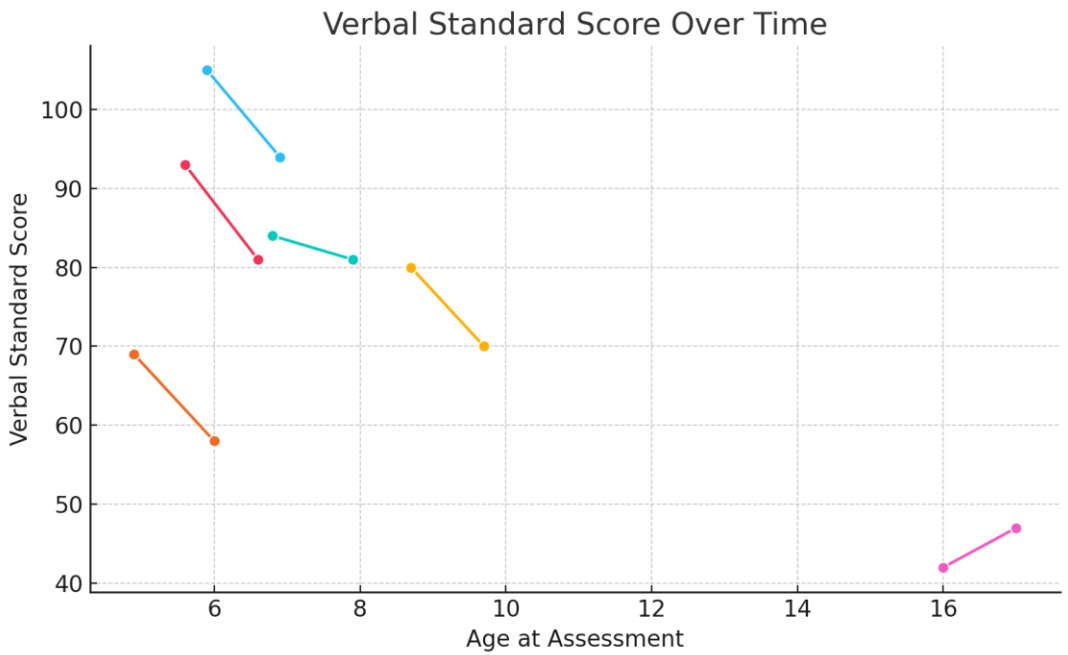
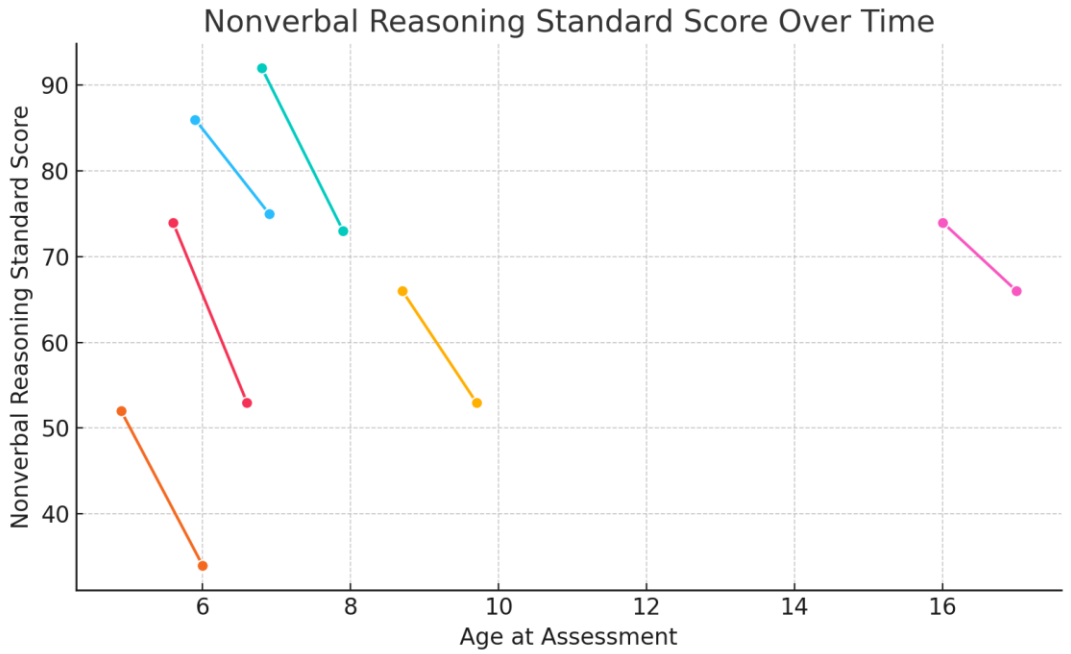
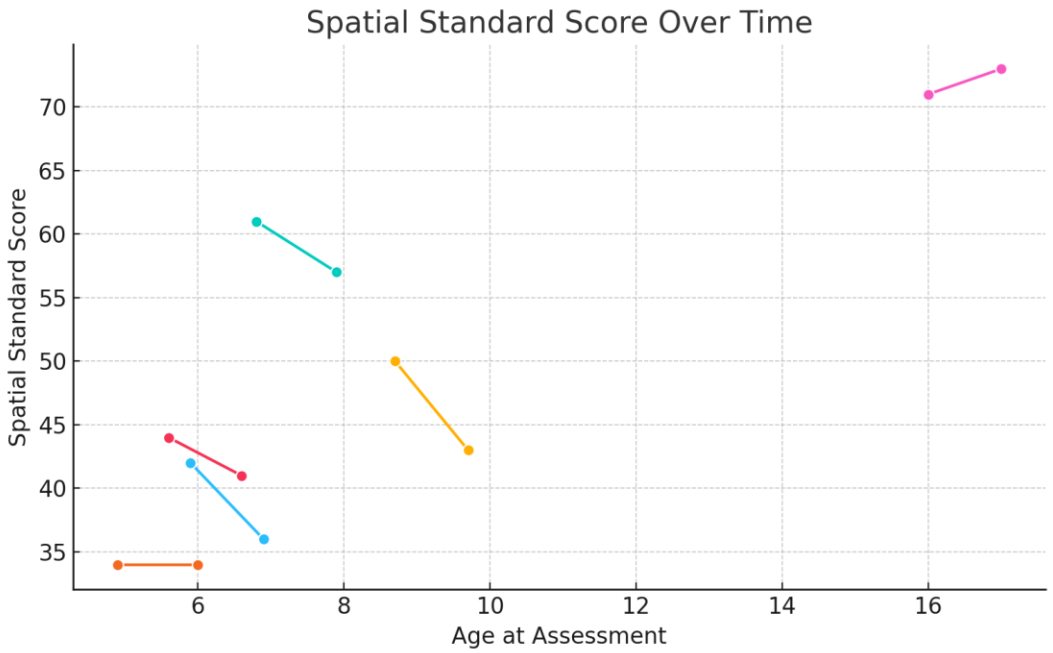
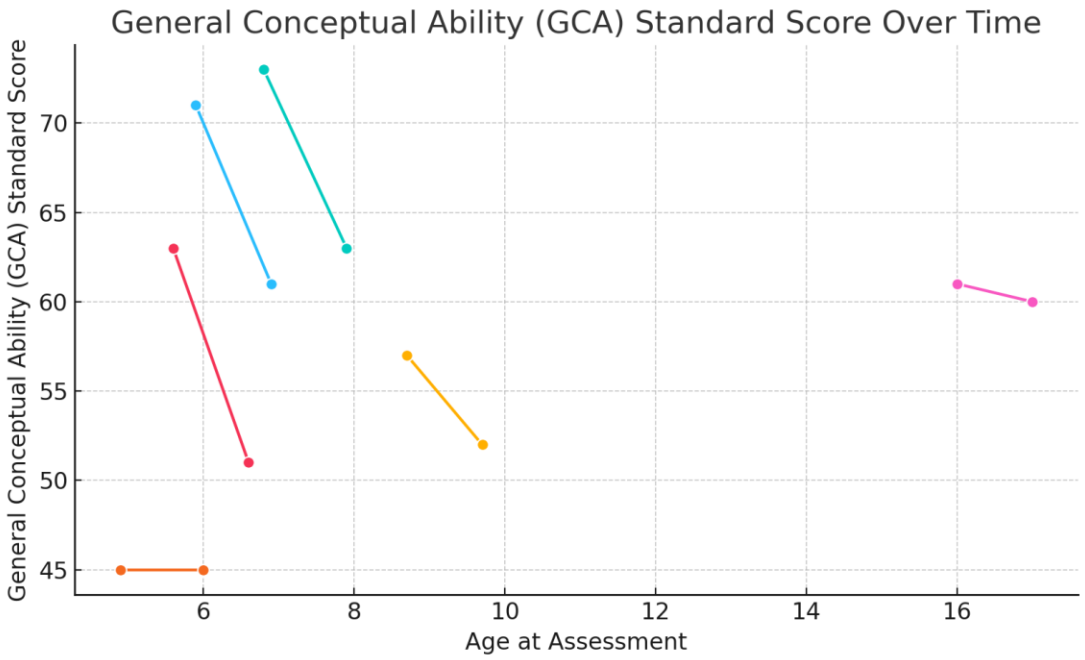
DAS-II Cognitive Assessment Longitudinal Scores

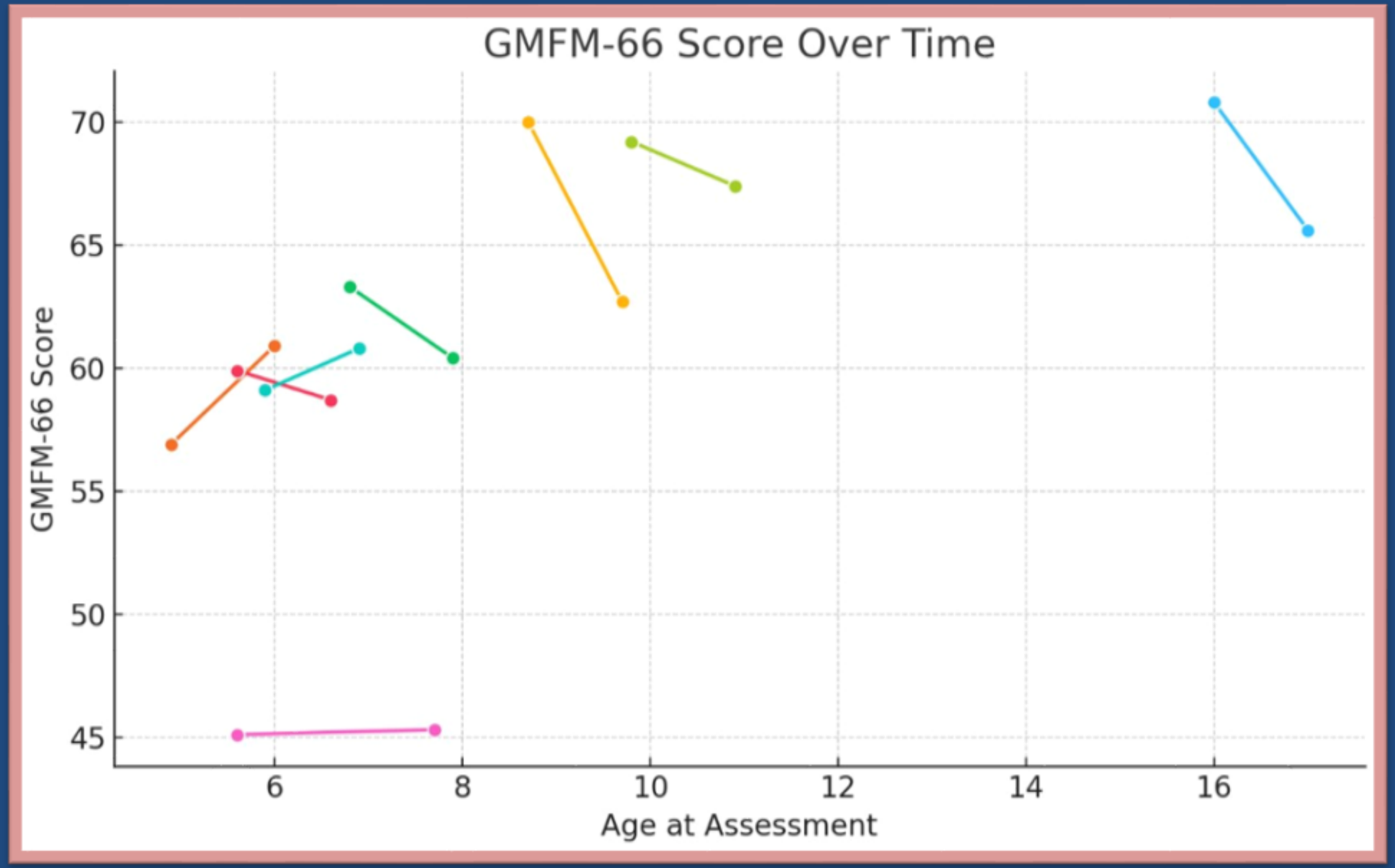




DAS-II Cognitive Assessment Longitudinal Scores






GMFM-66 Score Over Time
GMFM-66 Score
70
65
60
55
50
45
6
8
10
12
14
16
Age at Assessment

Summary: CTNNB1 Medical and Behavioral Phenotypes

Common issues

Intellectual disability/developmental delay
Language delay/impairment
Neurological issues
    Low muscle tone
    Small head size
    High muscle tone
Vision issues
    Farsightedness
    Crossed eyes

Other issues

- Autism
- Coordination Problems
- Cerebral Palsy
- Scoliosis
- Demands frequent attention
- Chewing on non-food items
- Adaptive behavior and development
- GI issues