

# The Unified Batten Disease Rating Scale

Jonathan W. Mink, MD PhD

Depts. of Neurology, Neurobiology & Anatomy,  
Brain & Cognitive Sciences, and Pediatrics

University of Rochester

# Batten Disease

- Neuronal Ceroid Lipofuscinosis
- Initially described by Batten in 1904 as juvenile-onset of a familial form of 'cerebral degeneration with macular changes' (familial amaurotic idiocy)
- Heterogeneous family of diseases with intracellular accumulation of autofluorescent lipopigment storage material in different ultrastructural patterns
- The clinical course includes progressive dementia, seizures, and progressive visual failure, but varied by type

# The Challenges

- Large clinical variability within each type of NCL and across the NCLs
- Progressive development of signs and symptoms over time
- Variable rates of progression
- The onset and progression occurs during times of developmental change

# A Good Clinical Rating Scale Must Have -

- Reliability – repeated measures yield the same results
- Validity – the scale actually rates what it is designed to rate
- Utility - the ability to test the observed behavior easily in a routine clinical setting

# The Unified Batten Disease Rating Scale (UBDRS)

- Demographics / Diagnostics / Medical History / Medications
- Physical Assessment
- Seizure Assessment
- Behavioral Assessment
- Capability Assessment
  - Assuming Normal Vision
  - Given Actual Vision
- Sequence of Symptom Onset
- Global Impression of Symptom Severity and Change Since Last Evaluation

# The UBDRS

- Developed and tested for Juvenile NCL, but was designed to be applicable to other NCLs with specific modifications
- Initial items for each subscale identified based on review of literature on clinical features of JNCL
- Additional items added based on experience from movement disorder rating scales
- Ongoing assessment of scale performance and reliability with modifications as guided by the data

# Subjects Since 2002

NUMBER OF EVALUATIONS	CLINICAL JNCL	CLN3 MUTATION	OTHER NCLs	UNDIAGNOSED	TOTAL EVALS
1	37	35	8	6	49
2	13	13	1	0	28
3	11	11	1	0	36
4	6	5	1	1	28
5	5	5	1	0	30
6	2	2	0	0	12
7	4	4	0	0	28
TOTAL SUBJECTS	78	75	12	7	---
TOTAL EVALUATIONS	185	179	22	10	211

# Physical Assessment

- Speech clarity
- Tongue protrusion
- Visual acuity
- Tone (arms, legs, neck)
- Strength (arms, legs)
- Hand tapping
- Heel stomping
- Spontaneous movements (akinesia)
- Stereotypies
- Dystonia
- Myoclonus
- Tremor
- Chorea
- Dysmetria
- Gait
- Postural stability

Each item scored 0 – 4. Maximum total score = 104.

# Seizure Assessment

- Generalized tonic/clonic seizures
  - Average frequency
  - Post-ictal period
- Atonic seizures
  - Average frequency
- Myoclonic seizures
  - Average frequency
- Complex partial seizures or Absence seizures
  - Average frequency
  - Post-ictal period
- Simple partial seizures
  - Average frequency
  - Average duration of event
- Frequency of injury related to seizures
- Maximal level of care for seizure complications
- Hospitalization required for treatment of seizures
- Anticonvulsant adjustment required in past month

Maximum total score = 54.

# Behavioral Assessment

- Sad mood
  - Frequency
  - Severity
- Apathy
  - Frequency
  - Severity
- Anxiety
  - Frequency
  - Severity
- Aggression toward others
  - Frequency
  - Severity
- Aggression toward self
  - Frequency
  - Severity
- Stereotyped/repetitive behavior
  - Frequency
  - Severity
- Compulsions
  - Frequency
  - Severity
- Obsessions
  - Frequency
  - Severity
- Auditory Hallucination
  - Frequency
  - Severity
- Medication required for behavior?

Each item scored 0 – 3 (except medication). Total 56 points.

# Capability Assessment

## ■ Assuming Normal Vision

- School
- Chores
- Play
- ADL
- Care level

## ■ Given Actual Vision

- School
- Chores
- Play
- ADL
- Care level

Total 28 points

# Clinical Global Impressions (CGI)

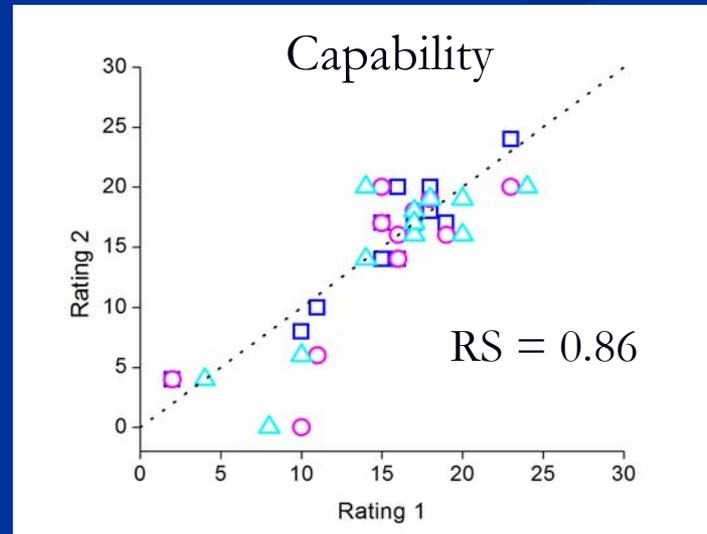
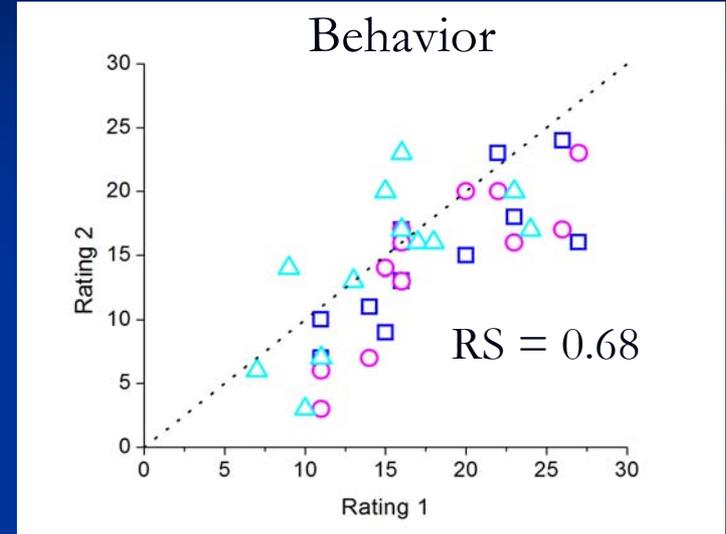
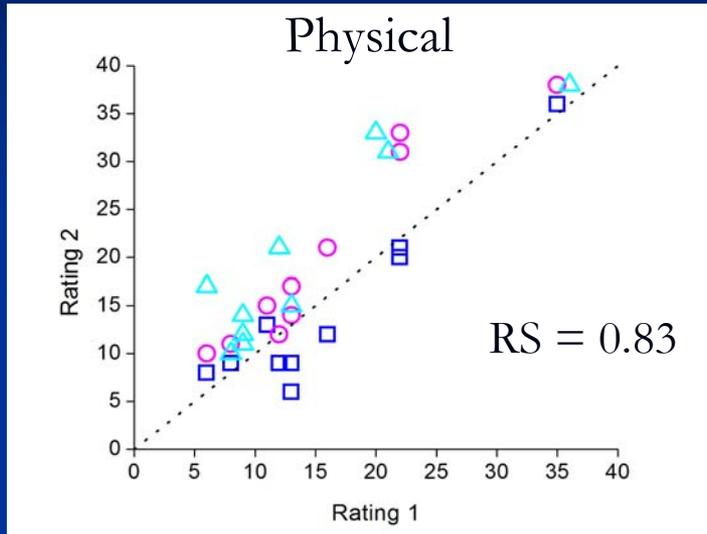
- Seizures
- Cognitive Function
- Behavior
- Mood
- Motor
- Overall
- Change since last assessment

Each rated on 0 – 5 scale.

# Scale Reliability

- Each subject examined by 3 neurologists independently, but in the same session
- Physical (motor), behavior, and capability scales treated as continuous variables
- Concordance calculated for each pair of examiners (Kendall)
- Winer reliability scores determined

# Inter-Rater Reliability



# A clinical rating scale for Batten disease

## Reliable and relevant for clinical trials

F.J. Marshall, MD; E.A. de Blicke, MPA; J.W. Mink, MD, PhD, FAAN; L. Dure, MD; H. Adams, PhD; S. Messing, MA, MS; P.G. Rothberg, PhD; E. Levy, BA; T. McDonough, BA; J. DeYoung, MD; M. Wang, BA; D. Ramirez-Montealegre, MD; J.M. Kwon, MD; and D.A. Pearce, PhD

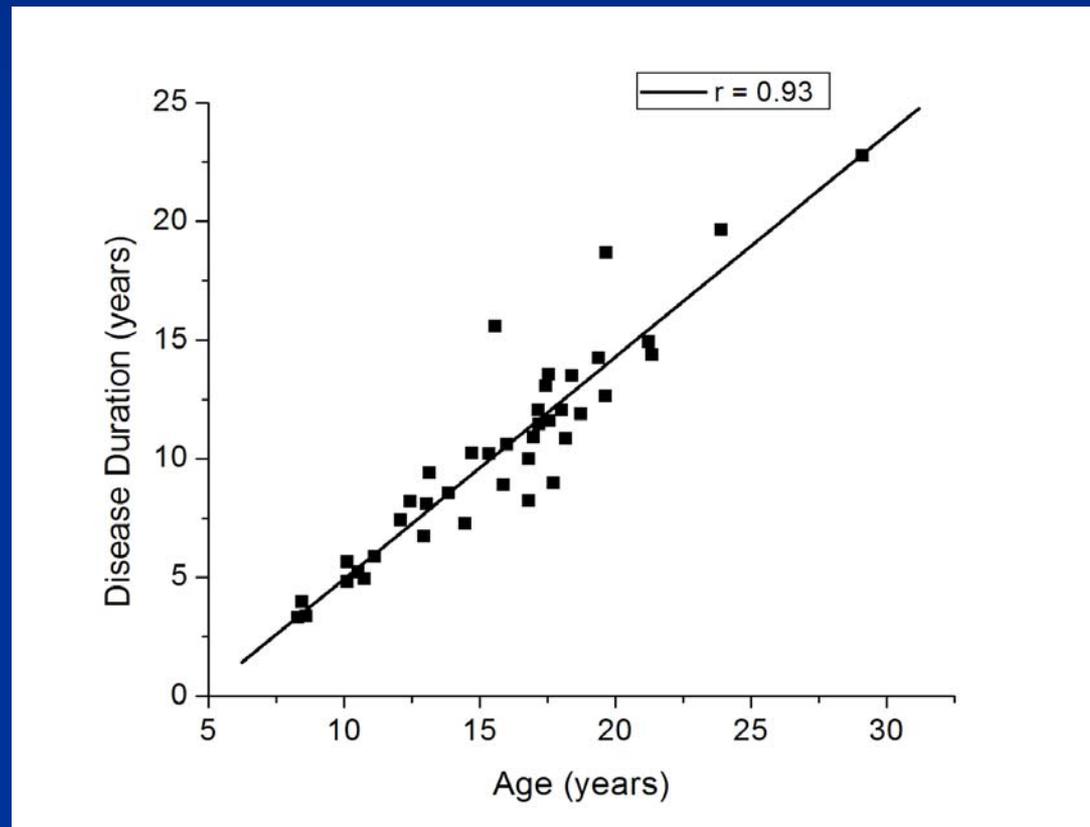
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**Abstract—Background:** Batten disease (juvenile neuronal ceroid lipofuscinosis [JNCL]) is an autosomal recessive neurodegenerative disorder characterized by blindness, seizures, and relentless decline in cognitive, motor, and behavioral function. Onset is in the early school years, with progression to death typically by late adolescence. Development of a clinical instrument to quantify severity of illness is a prerequisite to eventual assessment of experimental therapeutic interventions **Objective:** To develop a clinical rating instrument to assess motor, behavioral, and functional capability in JNCL. **Methods:** A clinical rating instrument, the Unified Batten Disease Rating Scale (UBDRS), was developed by the authors to assess motor, behavioral, and functional capability in JNCL. Children with verified JNCL were evaluated independently by three neurologists. Interclass correlation coefficients (ICCs) were used to estimate the interrater reliability for total scores in each domain. Interrater reliability for scale items was assessed with weighted  $\kappa$  statistics **Results:** Thirty-one children with confirmed JNCL (10 boys, 21 girls) were evaluated. The mean age at symptom onset was  $6.1 \pm 1.6$  years, and the mean duration of illness was  $9.0 \pm 4.4$  years. The ICCs for the domains were as follows: motor = 0.83, behavioral = 0.68, and functional capability = 0.85. **Conclusions:** The Unified Batten Disease Rating Scale (UBDRS) is a reliable instrument that effectively tests for neurologic function in blind and demented patients. In its current form, the UBDRS is useful for monitoring the diverse clinical findings seen in Batten disease.

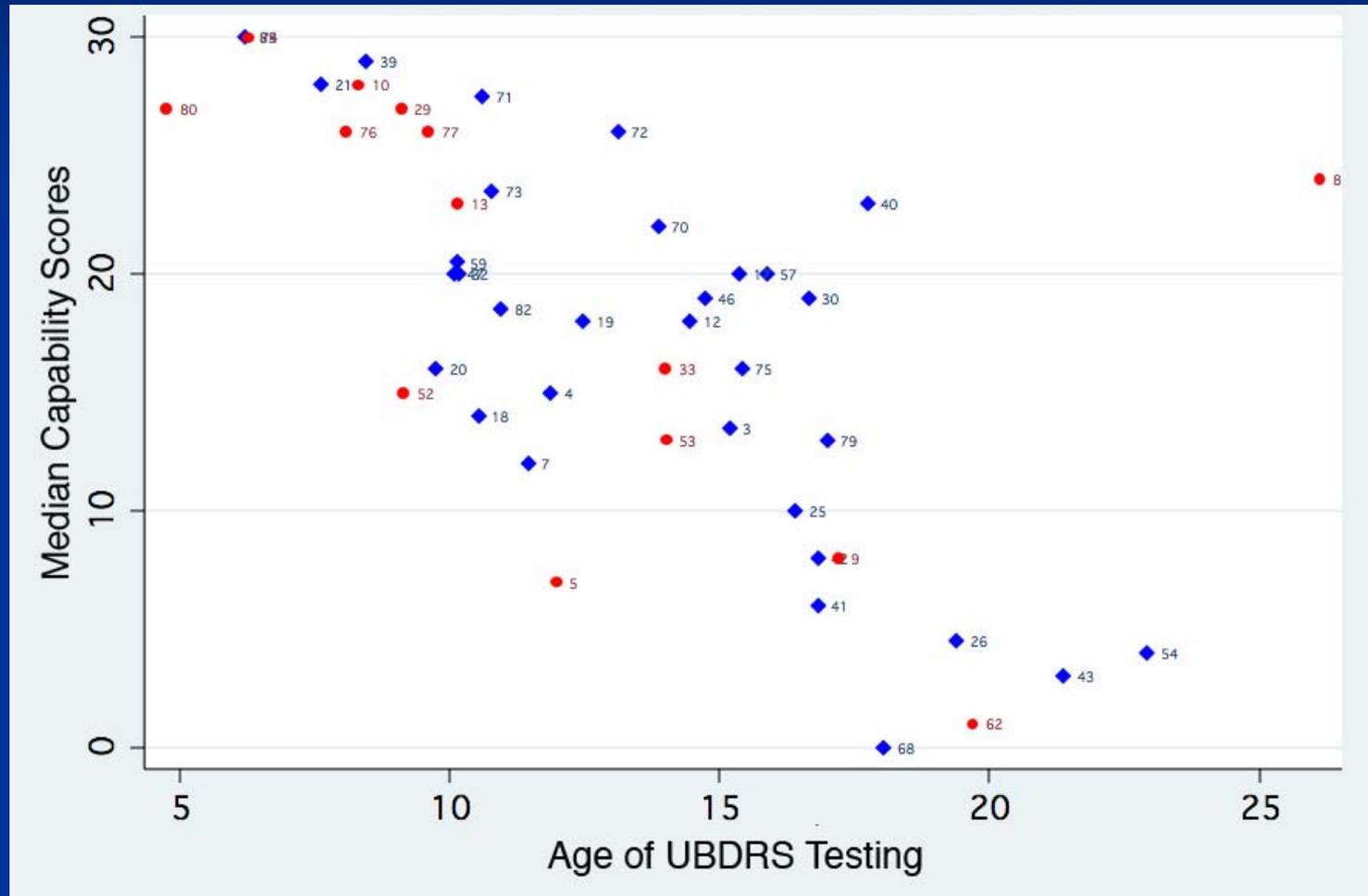
# Validity

- *Face Validity*: the measure is reasonable and likely to yield the type of information it was designed to obtain
- *Discriminative Validity*: lack of a relationship among measures that should not be related
- *Convergent Validity*: agreement among theoretically related ratings
- *Cross Validity*: agreement with previously validated measures

# Age as Surrogate for Progression

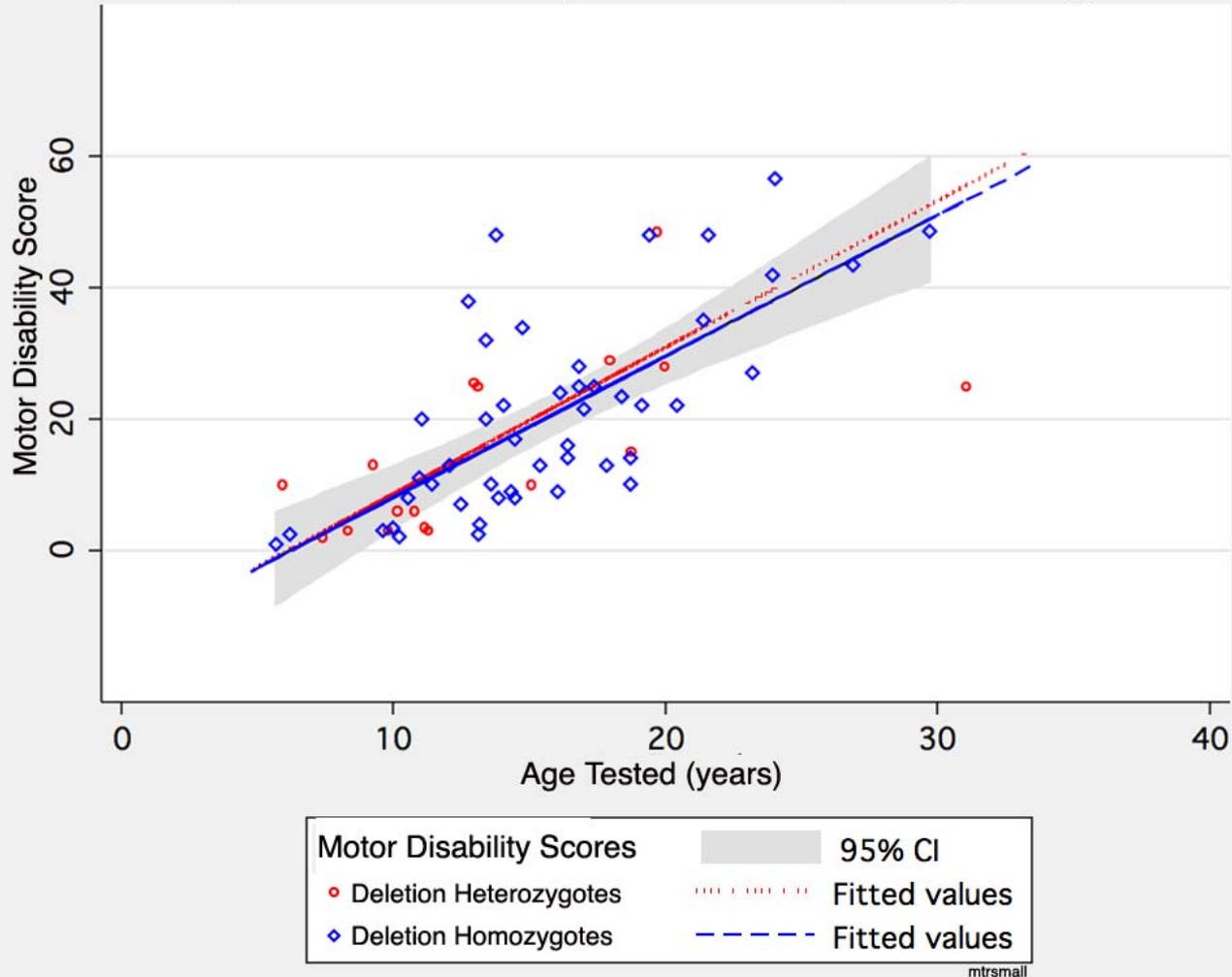


# Validity: Capability Scale

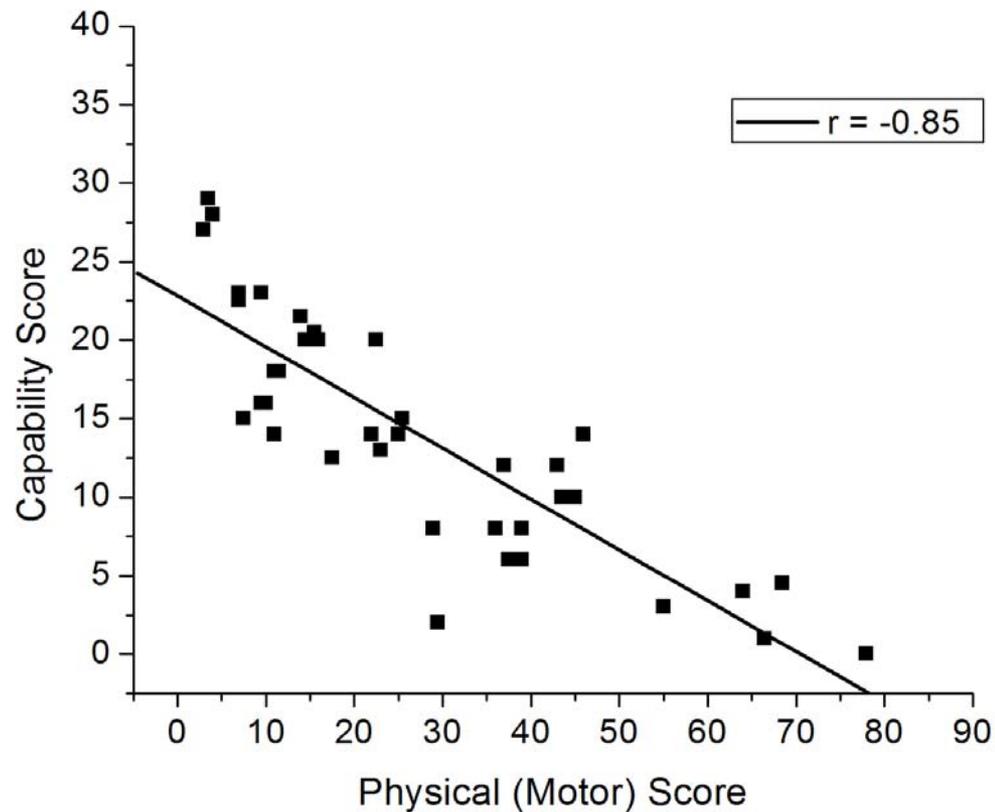


# Physical (Motor) Scale

Figure 2. Motor Disability Scores Increase (Worsen) with Age



# Convergent Validity: Physical and Capability Scales



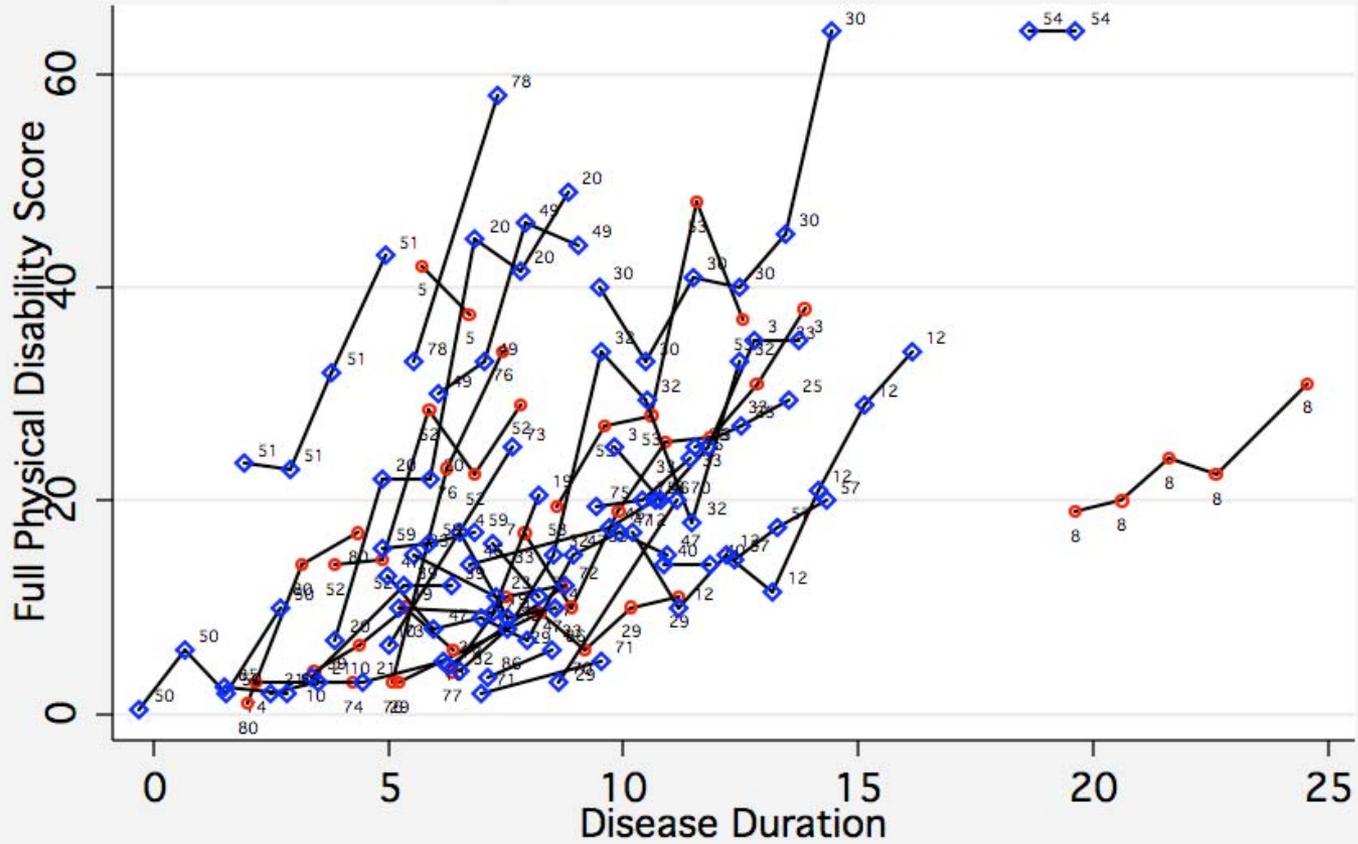
# Utility

- Entire instrument can be administered in 45 minutes
- Rating scale (excluding demographics and medication list) can be administered in 20 minutes
- Well-tolerated by children and parents

# So we have a tool . . .

- What can we learn about the disease?
- Is there a genotype – phenotype correlation?
- Is our scale sensitive to change over time so that we can use it to predict disease progression?
- What about treatment?

### Subjects seen more than once



—●— Other CLN3 mutations —◆— CLN3 deletion homozygotes

# The Team

- Neurologists
  - Erika Augustine, MD
  - Leon Dure, MD
  - Jennifer Kwon, MD, MPH
  - Frederick Marshall, MD
  - Jonathan Mink, MD, PhD
- Neuropsychologist
  - Heather Adams, PhD
- Statistician
  - Michael McDermott, PhD
  - Chris Beck, PhD
- Research coordinators
  - Elisabeth de Blicck, MPA
  - Nicole Newhouse
- Clinical Coordinator
  - Amy Vierhile, RN, PNP
- Students
  - Rachel Jordan
  - Erika Levy
  - Tiffani McDonough
  - Denia Ramirez
  - Sabrina Seehafer
  - Erin Stachowski
  - Melissa Wang
- Molecular Geneticist
  - Paul Rothberg, PhD
- Instigator
  - David Pearce, PhD

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