GOLISANO CHILDREN'S HOSPITAL

Review of UBDRS in JNCL: Reliability, Validity, and Endpoints

Jonathan W. Mink, MD PhD

Departments of Neurology, Neurobiology & Anatomy, Brain & Cognitive Sciences, and Pediatrics

University of Rochester

UNIVERSITY of ROCHESTER MEDICAL CENTER

MEDICINE of THE HIGHEST ORDER

Development of Outcome Measures

Identify and track biomarkers

Identify and track endophenotypes

Measure and follow clinical features

- Quantifiable measurements
- Clinical rating scale

The Unified Batten Disease Rating Scale (UBDRS)

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

Item elimination and modification based on initial reliability testing (Marshall et al., 2005)

Continued assessment of scale performance and reliability with modifications as guided by the data

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

Subject Ascertainment

Establish registry of known cases (2001 -)

Travel to Annual Batten Disease Support and Research Association (BDSRA) family meeting (2002 -)

Establish Batten Disease Clinical Research Center at University of Rochester (2005 -)

- Now a BDSRA Center of Excellence

All subjects genotyped at University of Rochester

Subjects 2002 - 2012

NUMBER OF EVALUATIONS	CLINICAL JNCL	CLN3 MUTATION	OTHER NCLs	UNDIAGNOSED	TOTAL SUBJECTS
1	49	45	10	4	63
2	12	11	3	1	16
3	11	11	0	0	11
4	5	5	1	1	7
5	3	3	0	0	3
6	5	5	2	0	7
7	5	5	0	0	5
8	2	2	0	0	2
9	2	2	0	0	2
10	3	3	0	0	3
11	1	1			11
TOTAL SUBJECTS	98	93	16	6	120
TOTAL EVALUATIONS	266	261	30	10	306

Clinical Features and Natural History of JNCL

Descriptive

- Age at onset
- Rate of Progression
  - Cross-sectional and longitudinal
  - Effect of CLN3 genotype
- Cognitive features

Hypothesis Testing

- Sex Differences

Use for retrospective evaluation of treatment

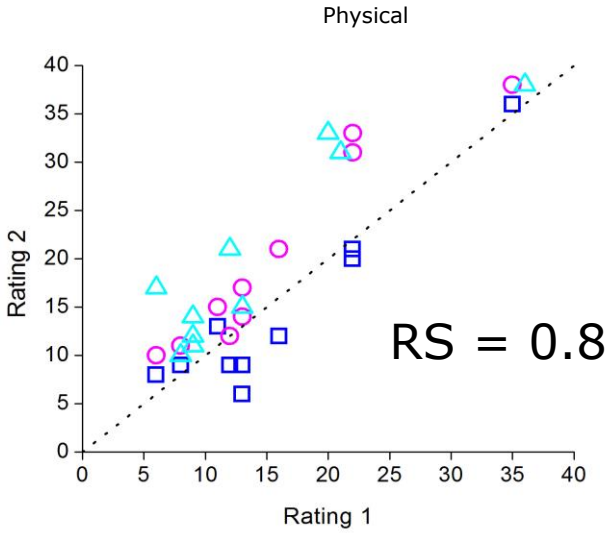
Baseline for clinical trials

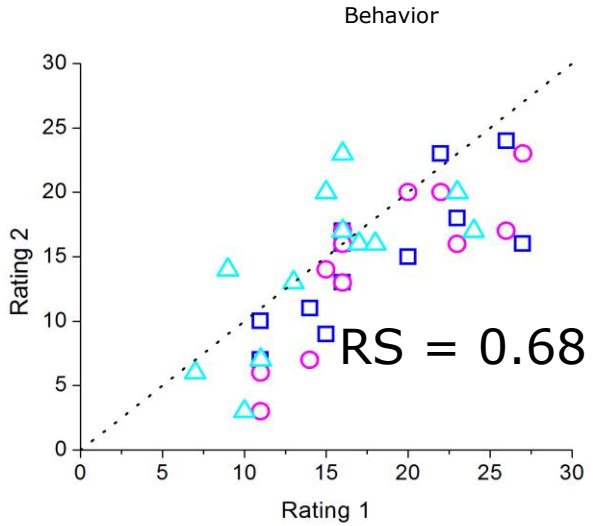
Average Age at Symptom Onset

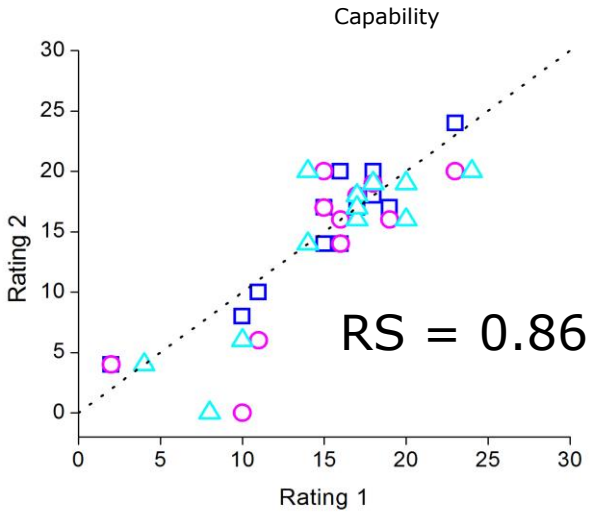
	Vision Loss	Behavior Problems	Cognitive Problems	Seizures	Motor Problems
Males	5.4 ± 1.5	7.0 ± 3.4	8.2 ± 4.0	9.8 ± 2.7	10.9 ± 4.4
Females	6.3 ± 1.4	9.5 ± 4.4	8.7 ± 2.9	9.4 ± 2.5	11.8 ± 3.6
	$P < 0.001$	$P < 0.05$	N.S.	N.S.	N.S.

Cialone et al, 2012

Inter-Rater Reliability

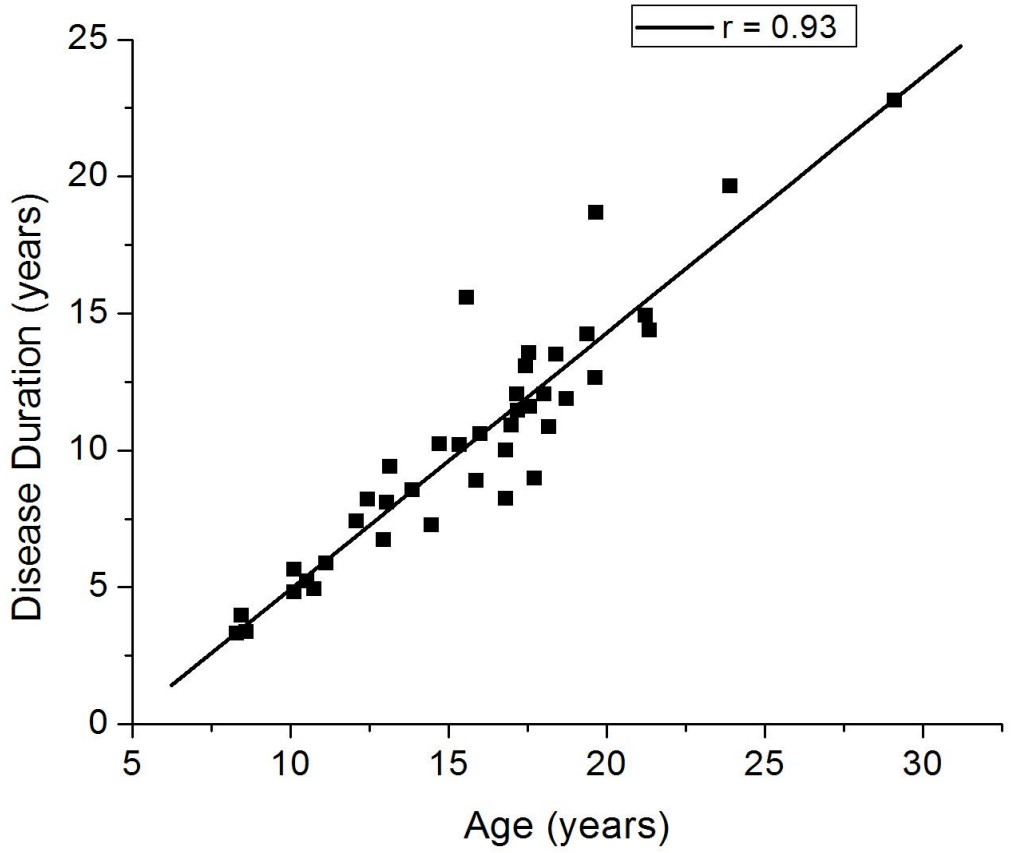




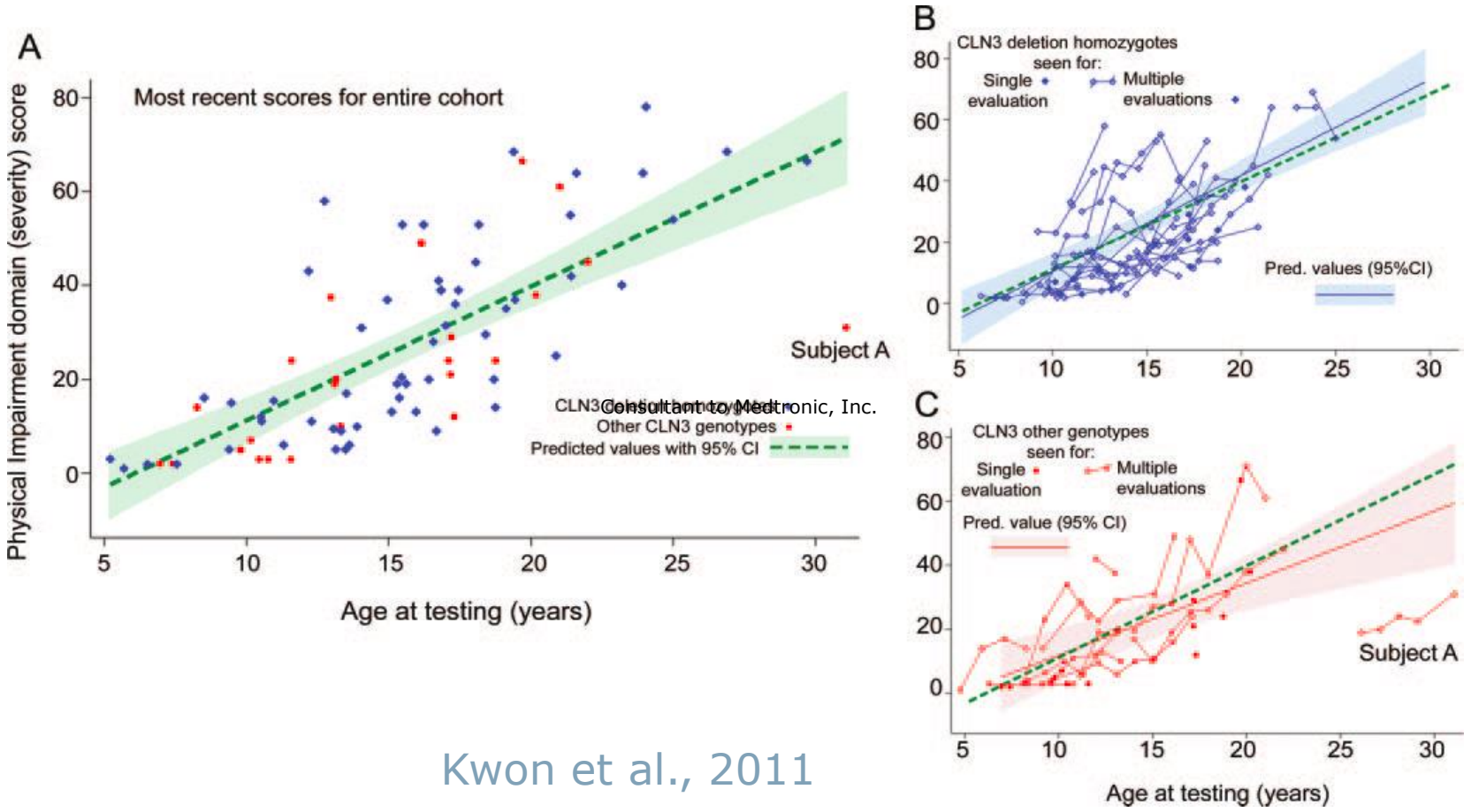


UNIVERSITY of ROCHESTER MEDICAL CENTER
Golisano Children's Hospital

Age as Surrogate for Progression



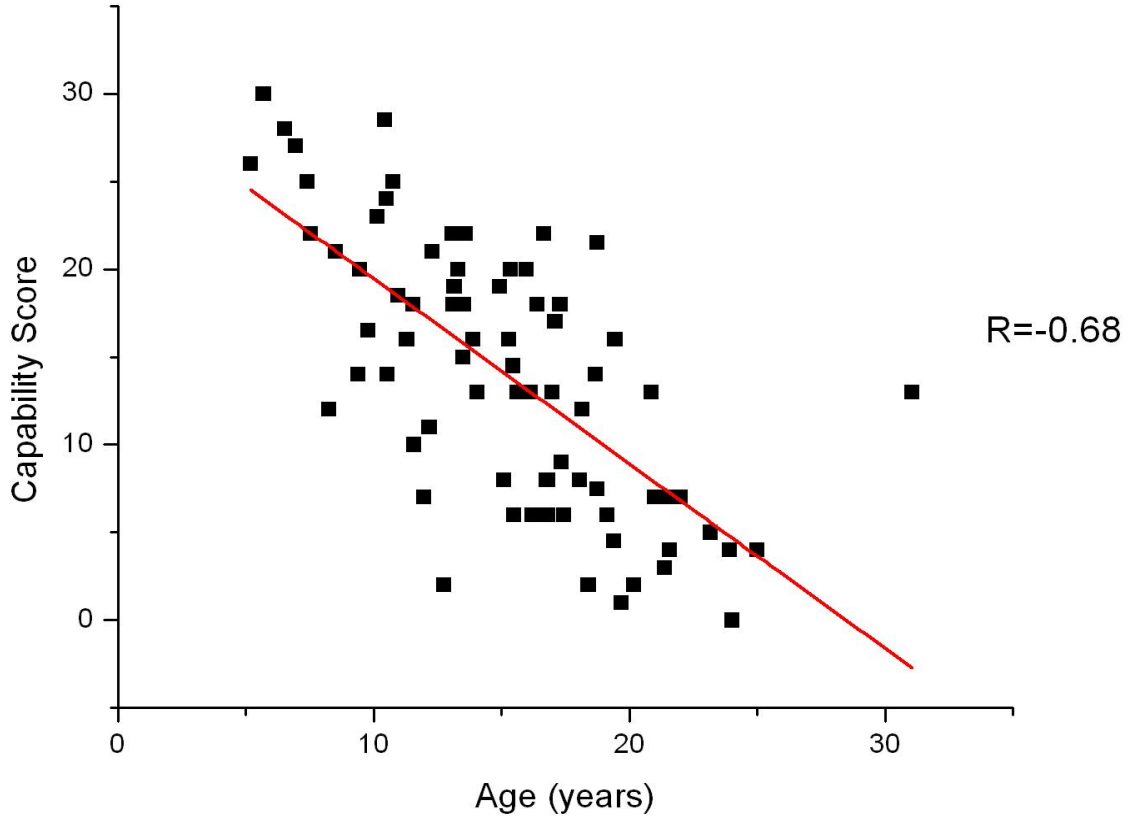
CLN3 Progression of Physical Impairment



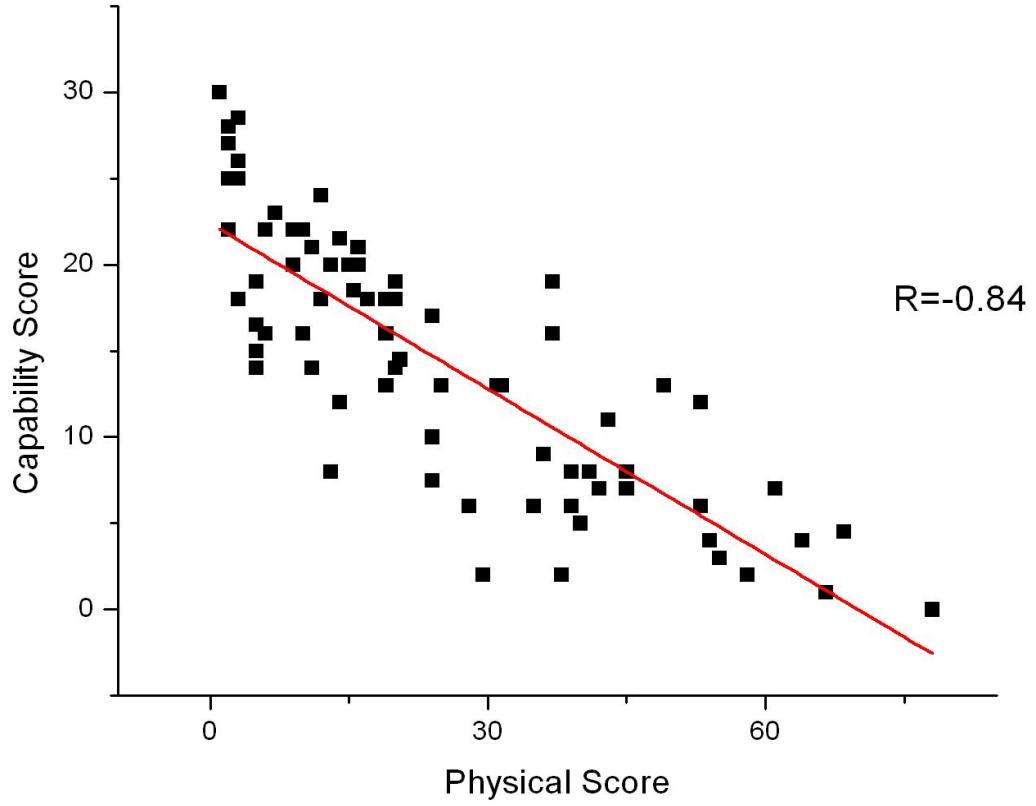
Consultant to Medtronic, Inc.

Kwon et al., 2011

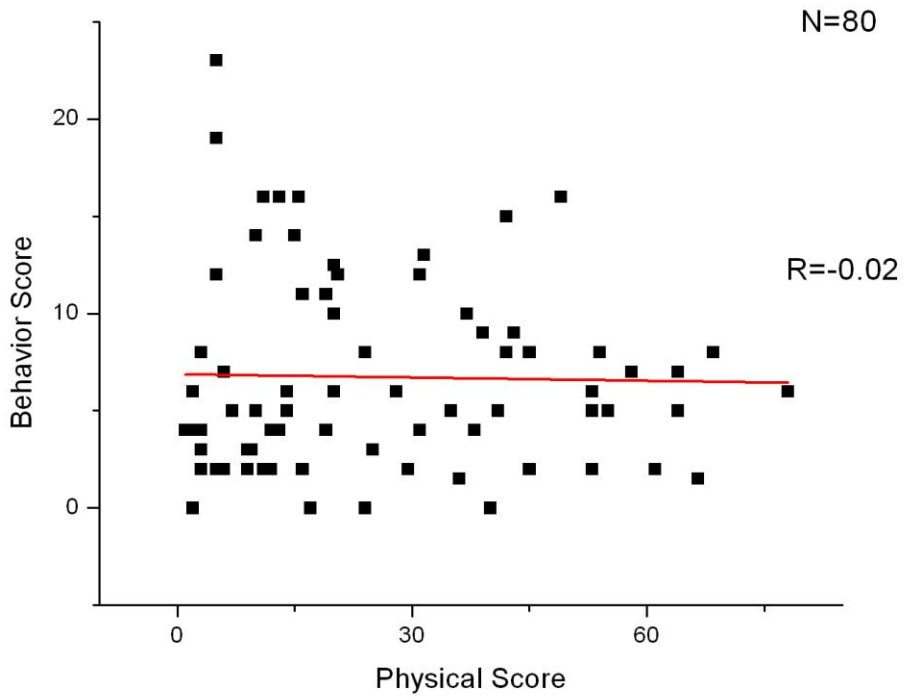
Capability Scale



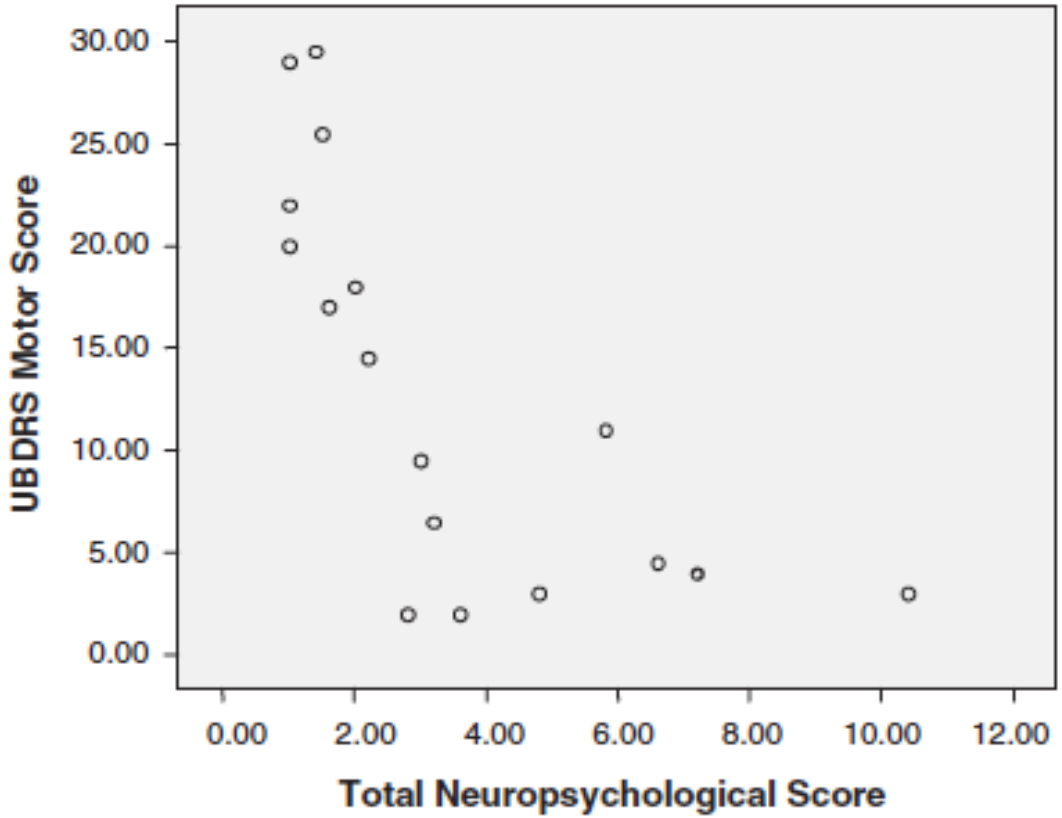
Convergent Validity: Physical and Capability Scales



Discriminative Validity: Behavior Scale

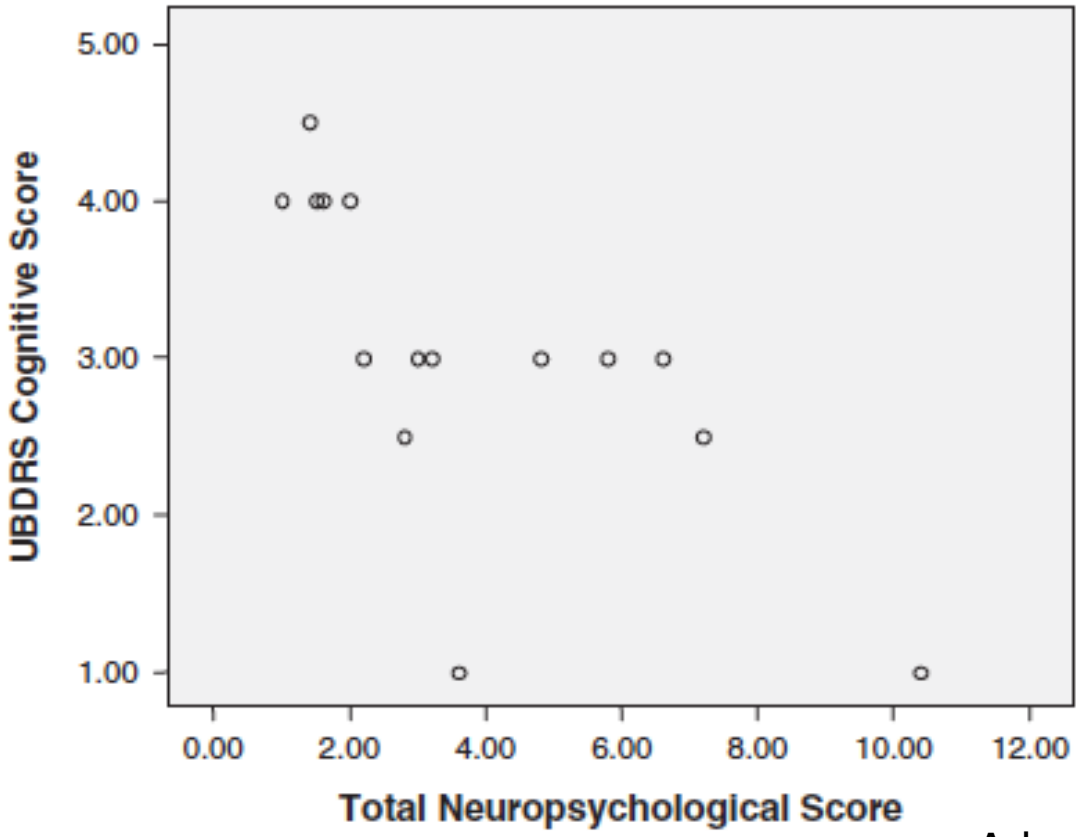


Physical Impairment vs. Cognitive Performance



Adams et al., 2007

Validation of UBDRS Cognitive CGI



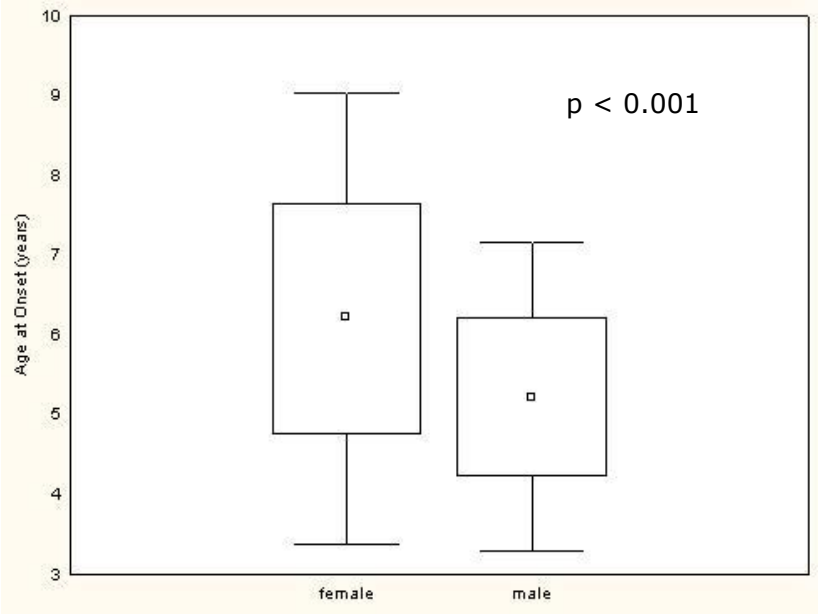
Adams et al., 2007

DO GIRLS HAVE A MORE SEVERE DISEASE TRAJECTORY THAN BOYS?

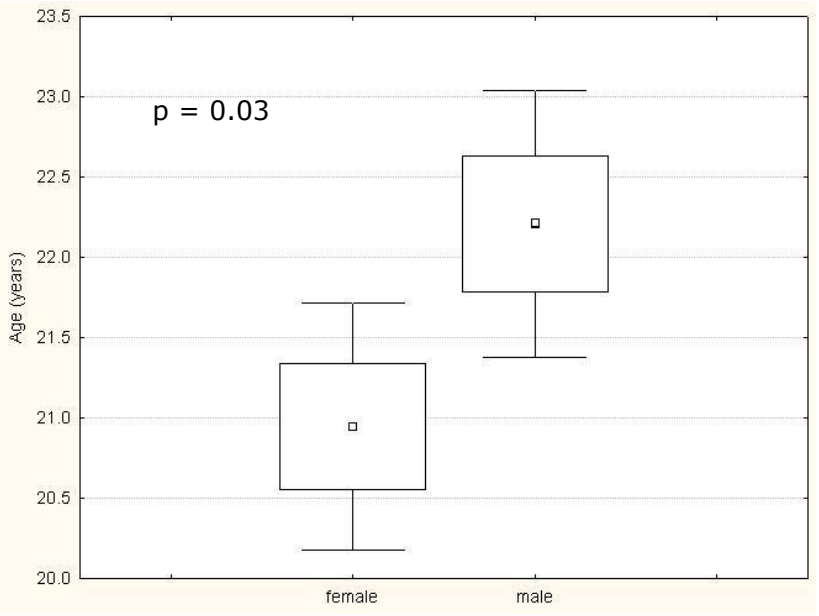
Endpoints from UBDRS and Elsewhere

JNCL Girls Have a Shorter Disease Course

Later Disease Onset

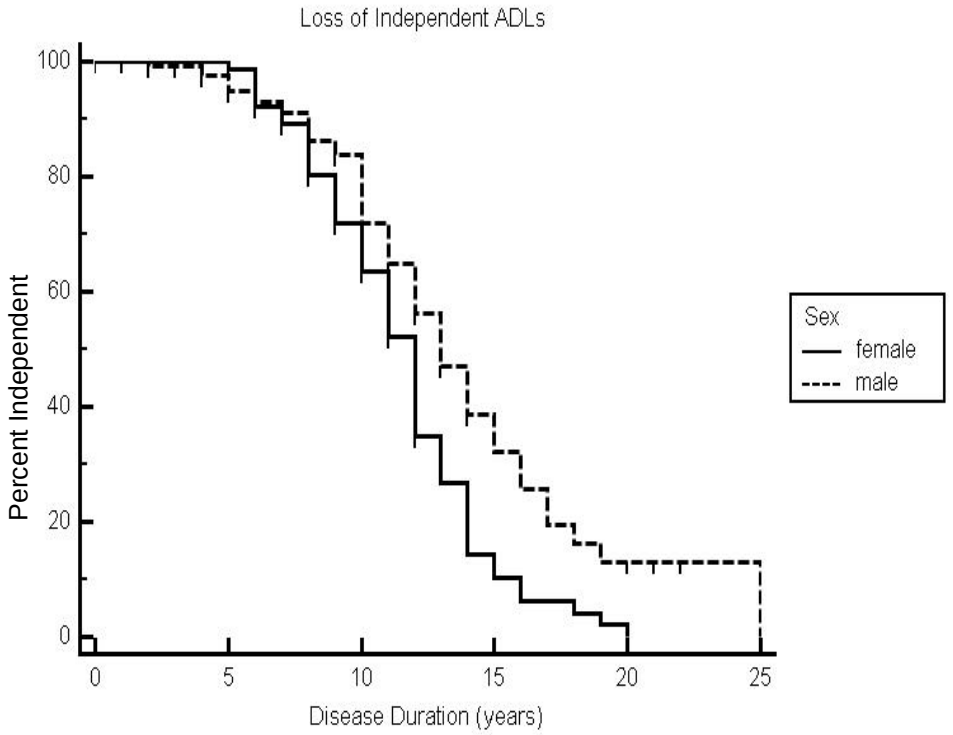


Earlier Death



Cialone et al., 2012

JNCL Girls Have Earlier Loss of Independent Function



Cialone et al., 2012

Summary – Sex Differences

Girls have a shorter duration of disease and earlier loss of independence, resulting in lower quality of life

Why?

- Female sex is often thought to be neuroprotective
- Role of autoimmunity?
- Sociocultural factors: what are society's expectations for girls?

Future Directions

- Look for other differences between girls and boys
- Better understanding of the molecular basis of the disease may lead to potential target for therapy

The Team

Neurologists
- Erika Augustine, MD
- Leon Dure, MD (UAB)
- Jennifer Kwon, MD, MPH
- Frederick Marshall, MD
- Jonathan Mink, MD, PhD
- Denia Ramirez, MD PhD

Neuropsychologist
- Heather Adams, PhD

Coordinators
- Elisabeth de Blieck, MPA
- Nicole Newhouse, RN
- Amy Vierhile, RN, PNP

Students
- Jennifer Cialone (MD)
- Rachel Jordan
- Erika (Levy) Wexler (MD)
- Tiffani McDonough (MD)
- Jennifer Riehl (MD)
- Katherine Rose
- Sabrina Seehafer (PhD)
- Melissa Wang (MD)

Statisticians
- Michael McDermott, PhD
- Chris Beck, PhD

Molecular Geneticist
- Paul Rothberg, PhD

Supported by BDSRA, NINDS, FDA OPD, RDCRN, URCTSI