

Gene Therapy for LINCL CSF Amendment

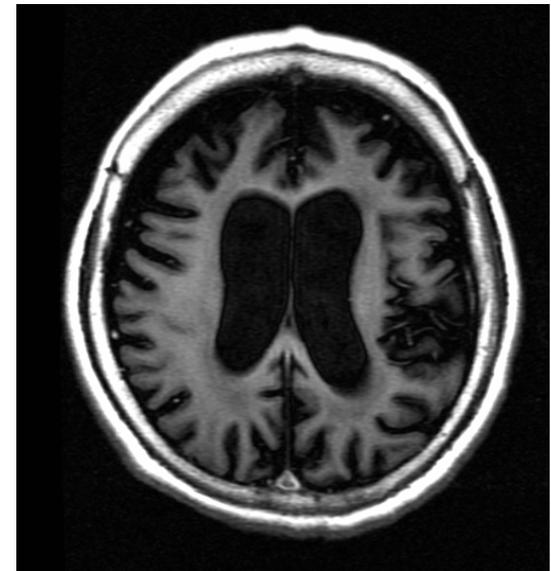
R. Crystal

Weill Cornell Medical College

9-16-10

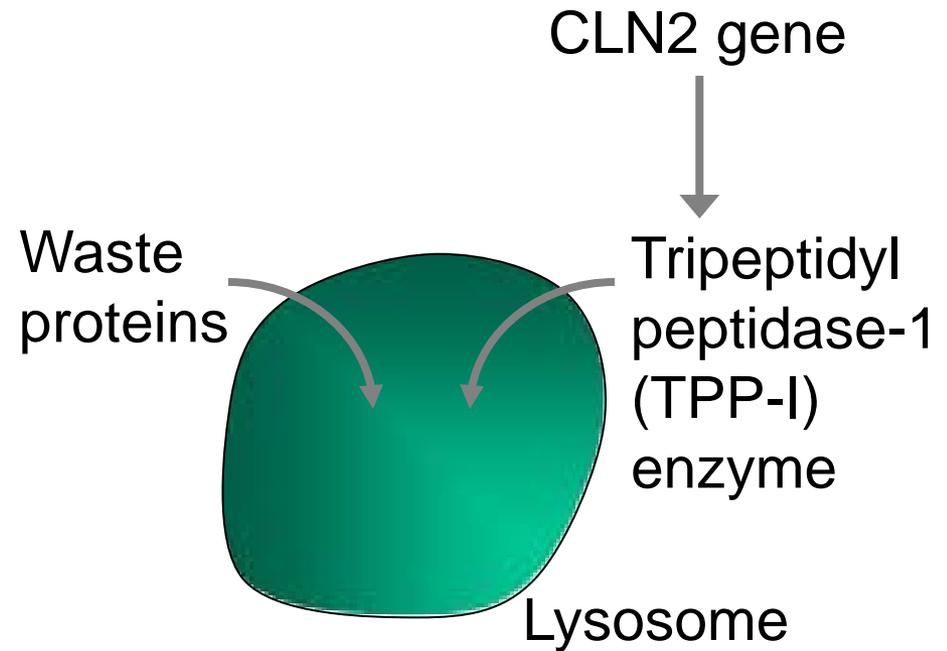
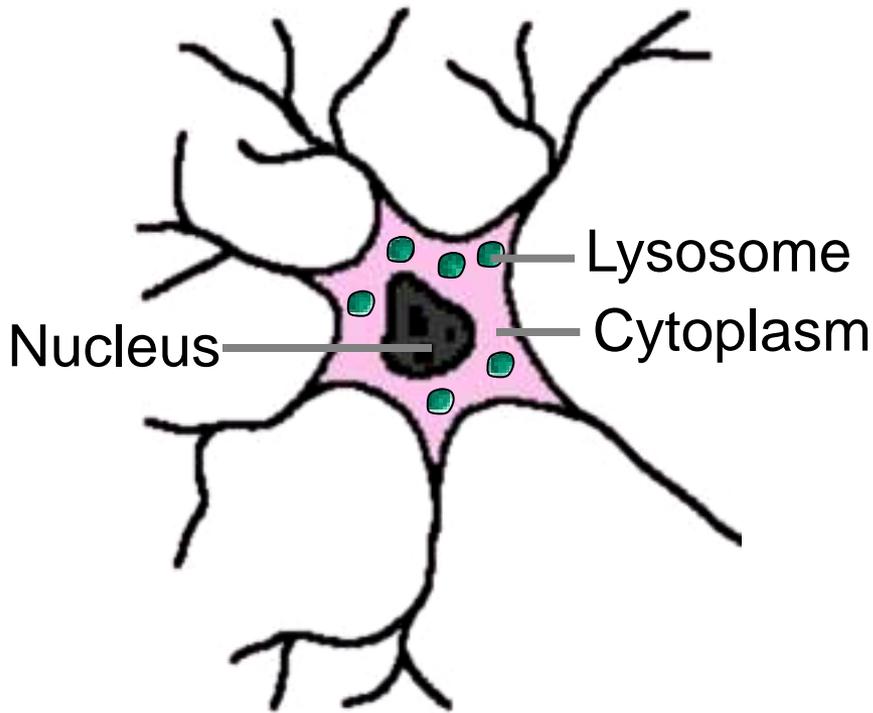
Late Infantile Neuronal Ceroid Lipofuscinoses (LINCL, Batten Disease)

- Autosomal recessive, 1 / 2 million births, ~ 200 cases worldwide
- Disease onset ages 2-4
- Cognitive impairment, visual failure, seizures, and deteriorating motor development, leading to a vegetative state and death by ages 8-12

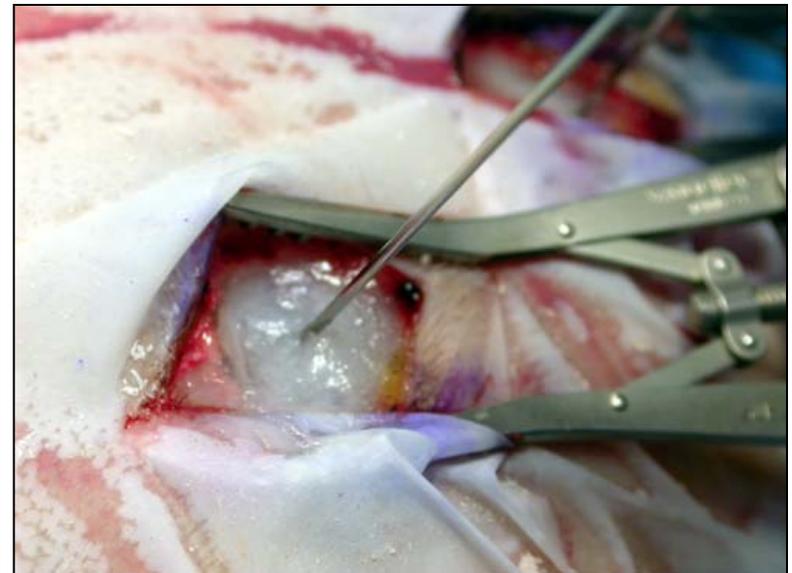
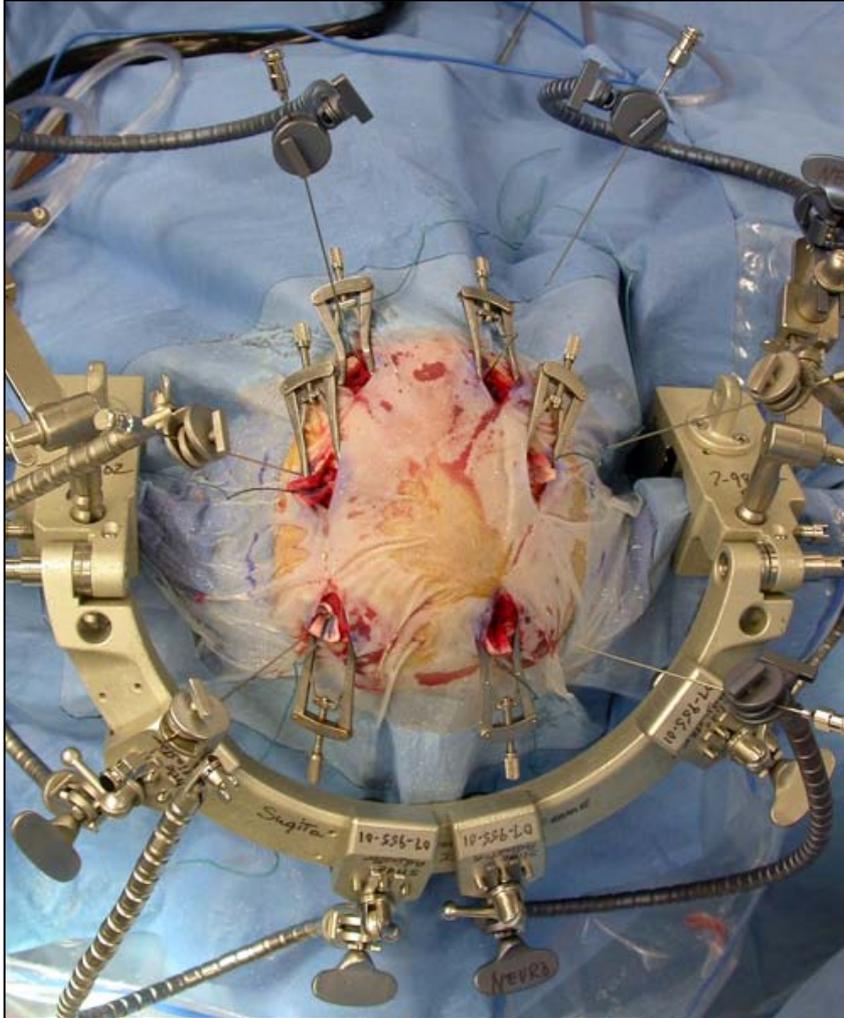


LINCL Is Caused by Mutations in the CLN2 Gene

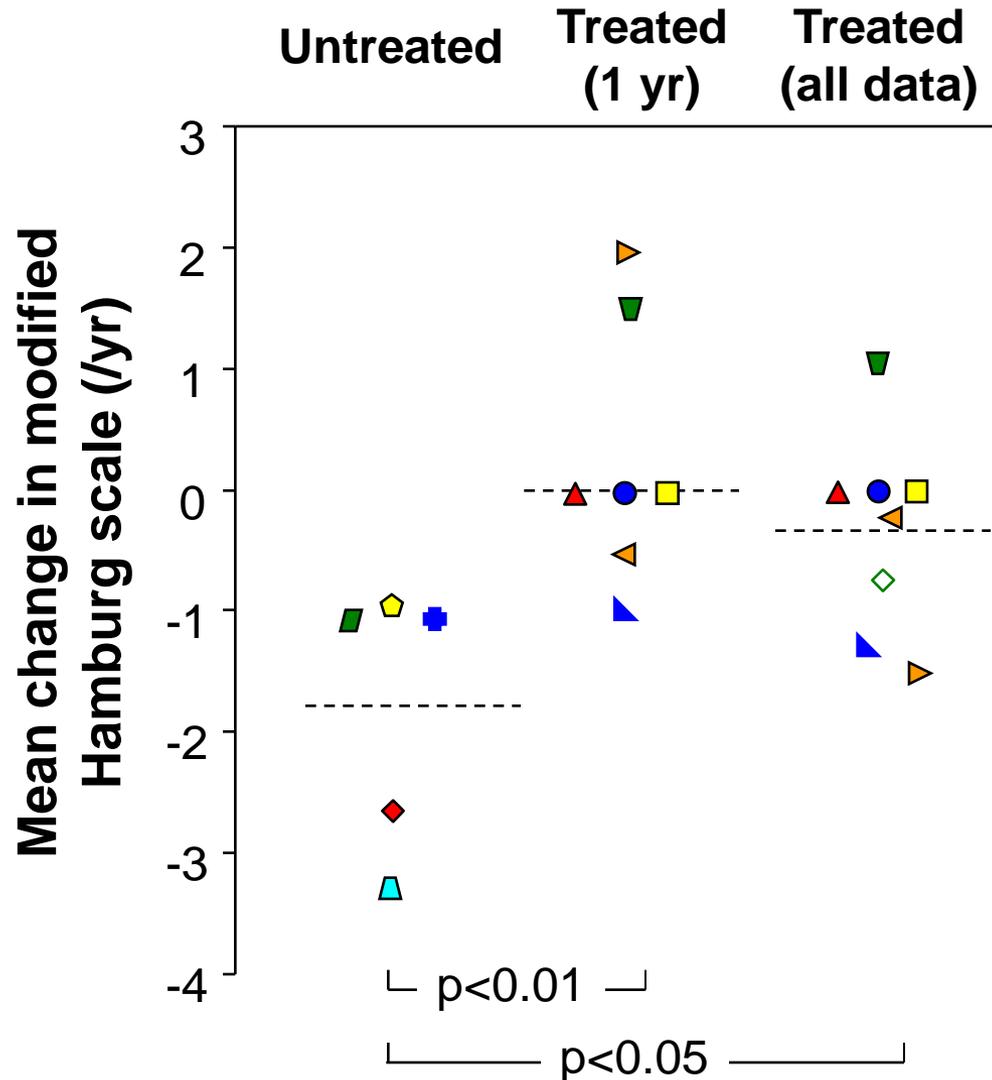
Neuron



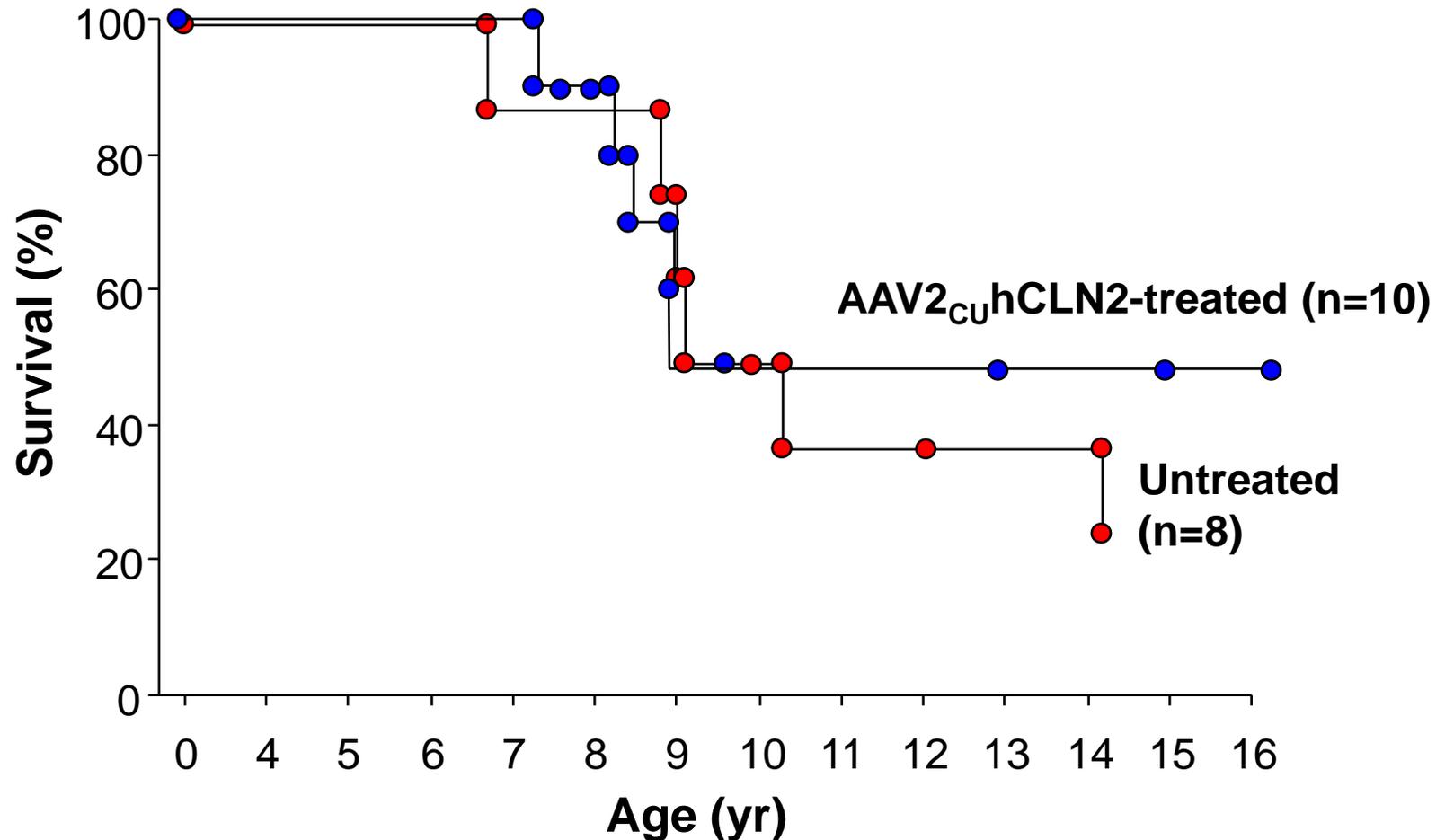
AAV Vector CNS Administration



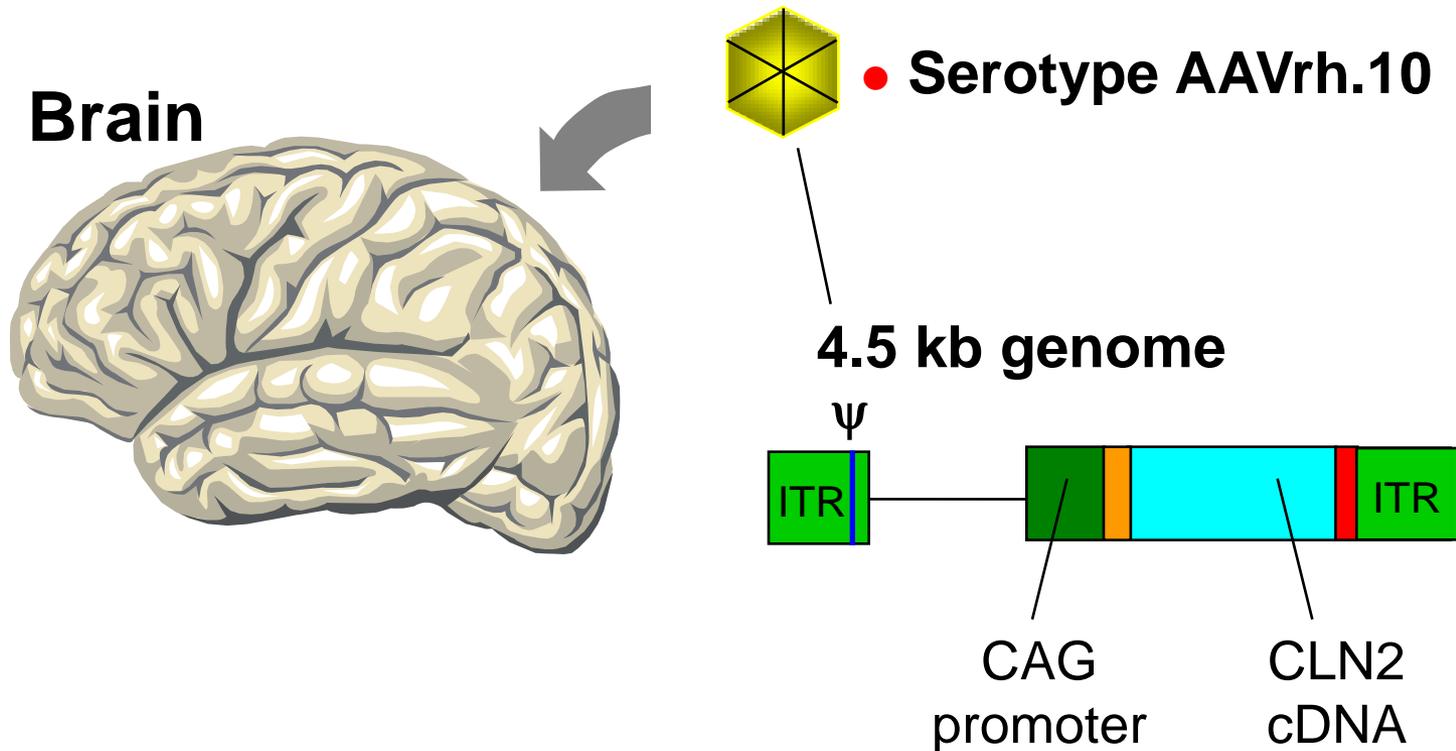
AAV2 Trial 1⁰ Variable – Modified Hamburg LINCL Scale



AAV2 Trial Post-therapy Survival Compared to Untreated Controls

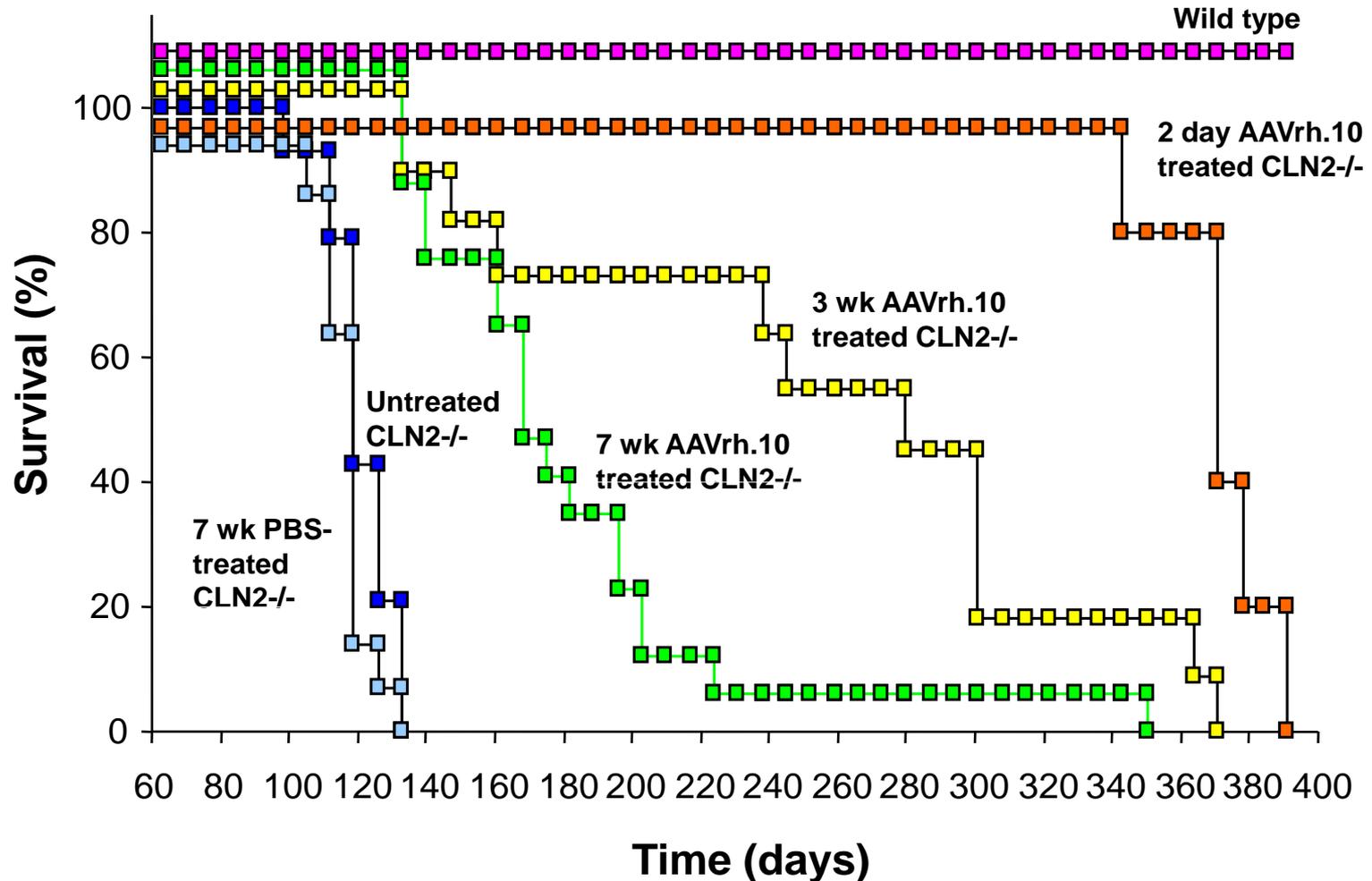


2nd Generation Gene Therapy for LINCL



- n=16 treated children with LINCL vs n=16 untreated children, all mild-moderate on the Weill Cornell scale

Survival of CLN2^{-/-} Mice Treated at Different Times with AAVrh.10hCLN2

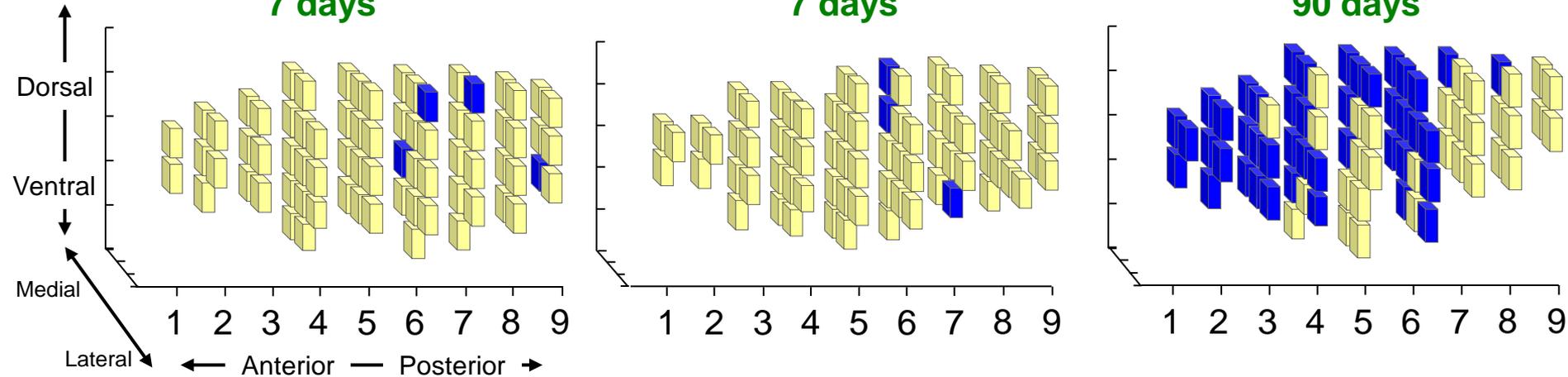


Distribution of TPP-I Activity in the CNS of Non-human Primates Following CNS Administration of AAVrh.10_{CU}hCLN2

NHP Y132
PBS
7 days

NHP 066
AAVrh.10_{CU}hCLN2
7 days

NHP 029
AAVrh.10_{CU}hCLN2
90 days



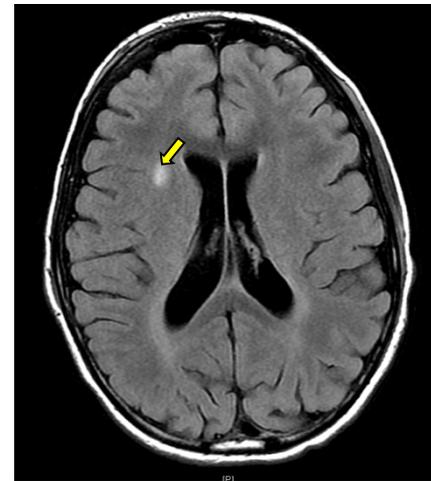
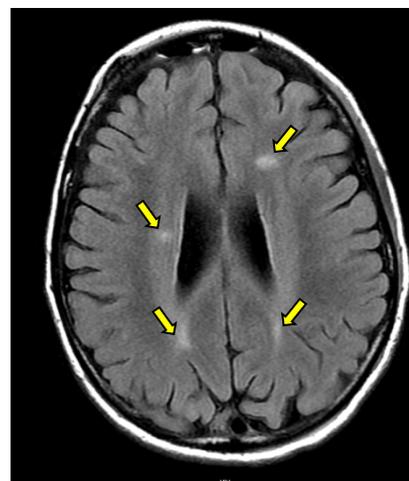
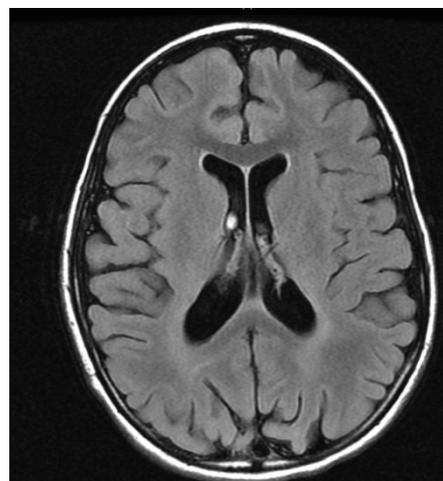
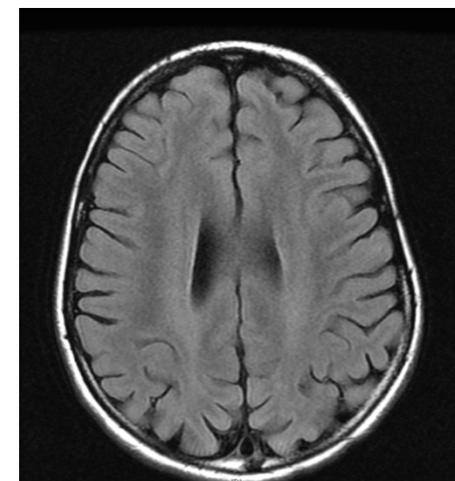
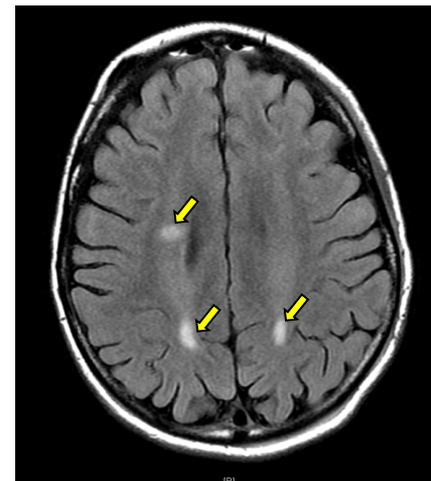
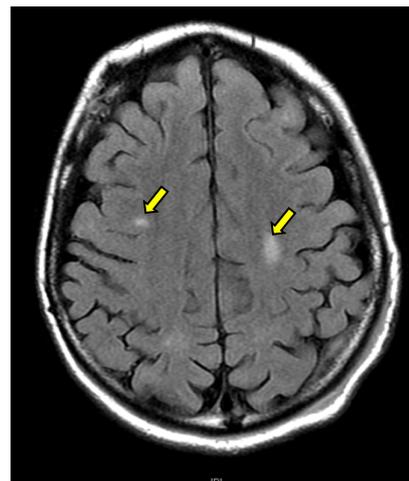
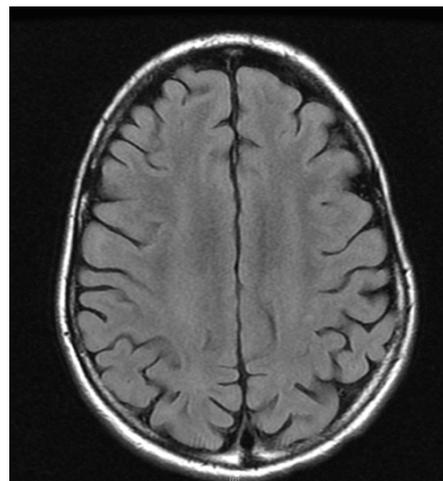
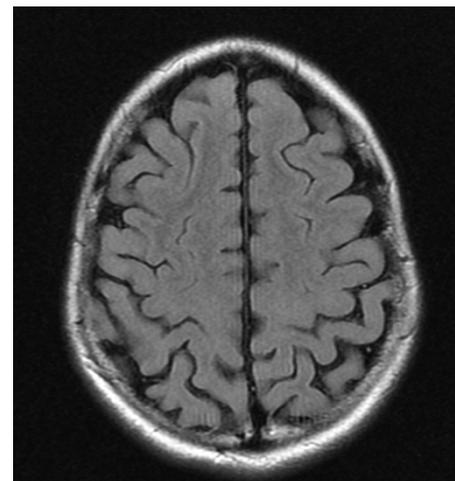
 <2 Standard deviations (SD)  >2 SD

Status of the AAVrh.10 Trial

- 1st child treated
- 7 yr 3 months
- CLN2 genotype G3556C homozygote
- Weill Cornell LINCL score 6.3
- 7.5×10^{10} genome copies/site, 12 sites, total dose 9×10^{11} genome copies
- No serious adverse events

BDrh-03-C-I MRI T₂ FLAIR Pre-Vector

Post-Vector 48 hr



Critical Path in Developing Therapies for Rare Disorders of the CNS

PHENOTYPE

Controls and Ethical Issues

- Fatal, childhood disease for which there is no therapy
- No pre-natal or newborn screening
- Therapy requires invasive, neurosurgical procedure
- Therapeutic misconception
- Challenge – what do we use as controls?
- Regulatory approval of efficacy is a giant hurdle

Overall Design of the Trial

Subject with LINCL

Screening protocol
(limit to 5 genotypes)

Not eligible

Eligible

Family given choice to continue in
screening protocol or enter
treatment protocol

Consent process
independent of PI, includes
CTSC patient advocate

Untreated
n=16

Assess efficacy parameters
at 18 months

Treatment with AAVrh.10hCLN2
n=16

1st dose cohort
n=8

7.5×10^{10} gc/site
12 sites

Total dose 9.0×10^{11} gc

Assess efficacy
parameters at 6, 12, 18
months

2nd dose cohort
n=8

1.5×10^{11} gc/site
12 sites

Total dose 1.8×10^{12} gc

Assess efficacy
parameters at 6, 12, 18
months

Decision by 4 faculty, representing
3 departments, independent of PI

Outcome Measures

Primary

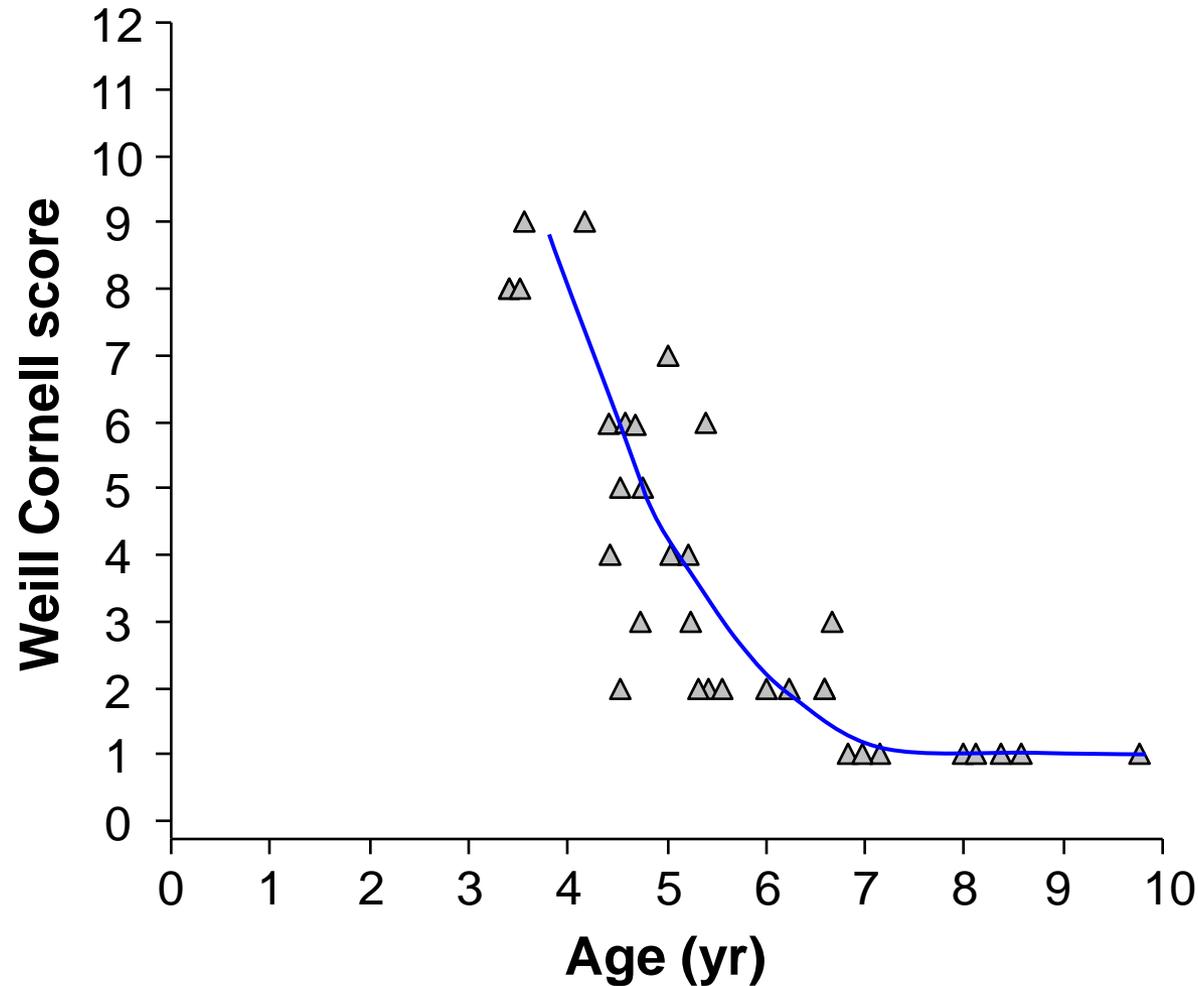
- Weill Cornell LINCL score¹
- Quantitative MRI
 - % Ventricular volume
 - % Grey matter volume
 - Cortical apparent diffusion coefficient

Secondary

- Mullen score
- CHQ Quality of Life questionnaire

¹ Feeding 0-3, gait 0-3, motor 0-3, language 0-3; assessed independently by 3 pediatric neurologists; total score = sum of score for the 4 parameters, 12 = normal, 0 = maximum impairment

LINCL Age-dependent Changes in the Weill Cornell LINCL Score

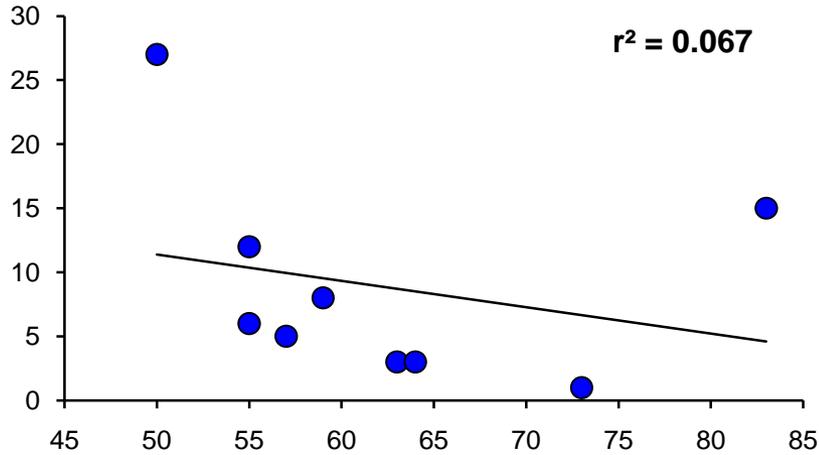


Variability in the Weill Cornell LINCL Score Among Blinded Neurologists

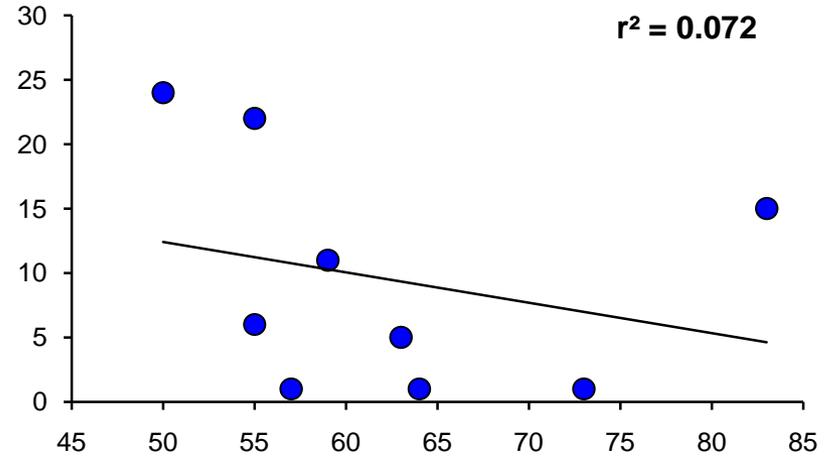
Subject	Scorer	Weill Cornell LINCL score				
		Total	Feeding	Gait	Motor	Language
BDrh-01-IW	Live neurologist	6	2	1	1	2
	Blinded # 1	6	2	0	2	2
	Blinded # 2	5	2	0	1	2
	Average	5.6	2	0.3	1.3	2
BDrh-02-IN	Live neurologist	9	3	2	2	2
	Blinded # 1	9	3	2	2	2
	Blinded # 2	9	3	2	2	2
	Average	9	3	2	2	2
BDrh-03-CI	Live neurologist	8	2	2	1	3
	Blinded # 1	7	2	1	3	1
	Blinded # 2	8	2	2	1	3
	Average	7.7	2	1.7	1.7	2.3

Mullen Scores

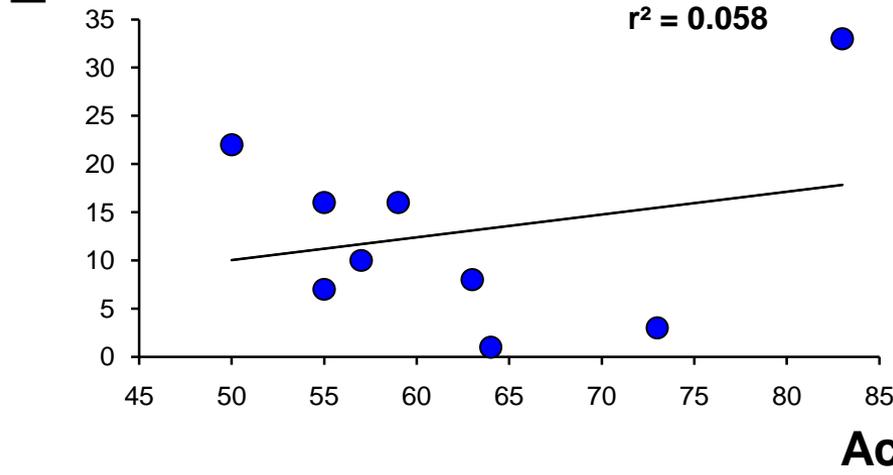
A. Gross motor



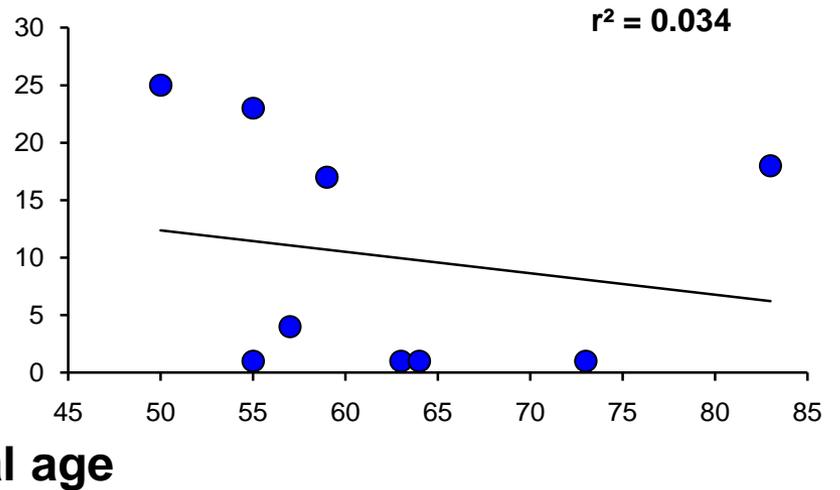
B. Fine motor



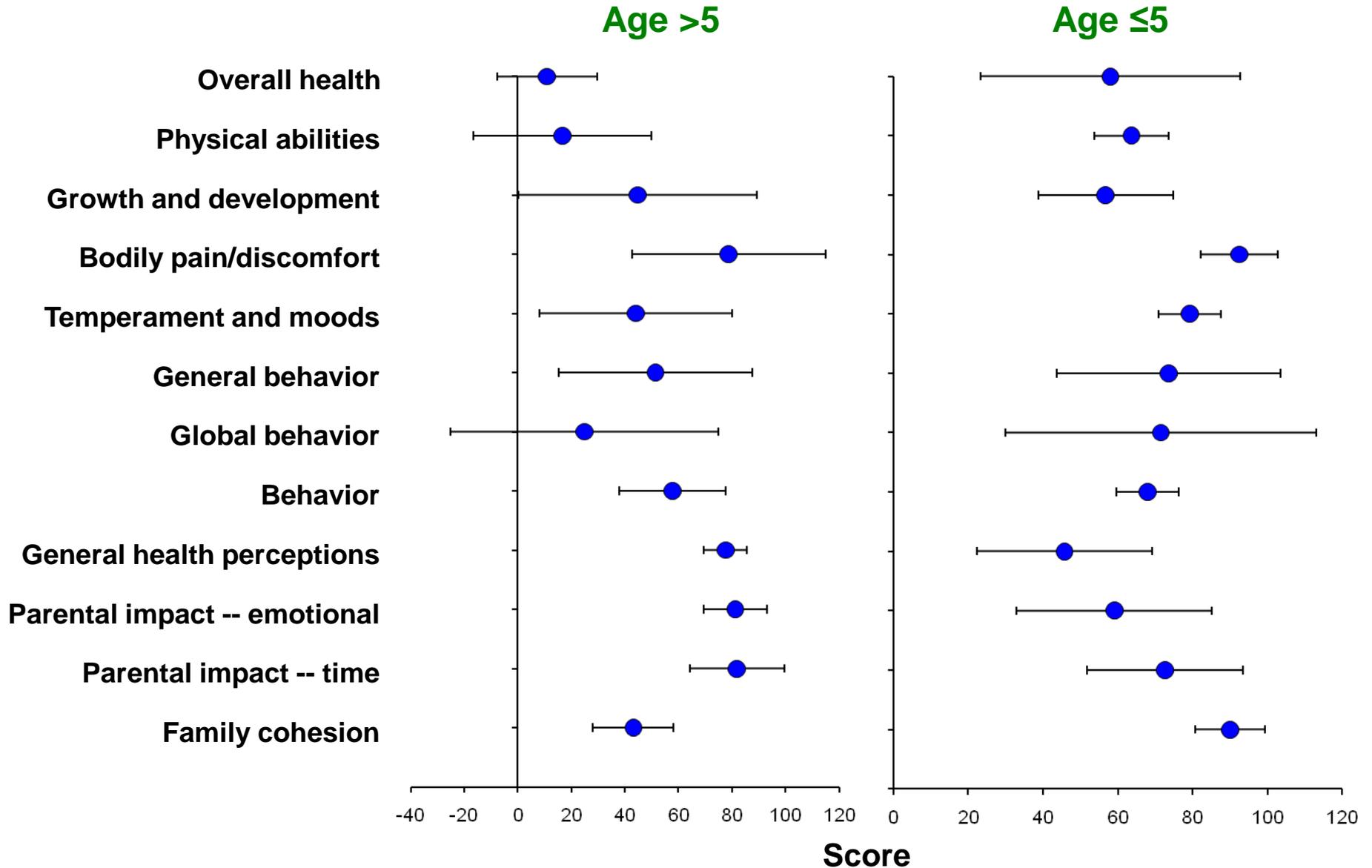
C. Expressive language



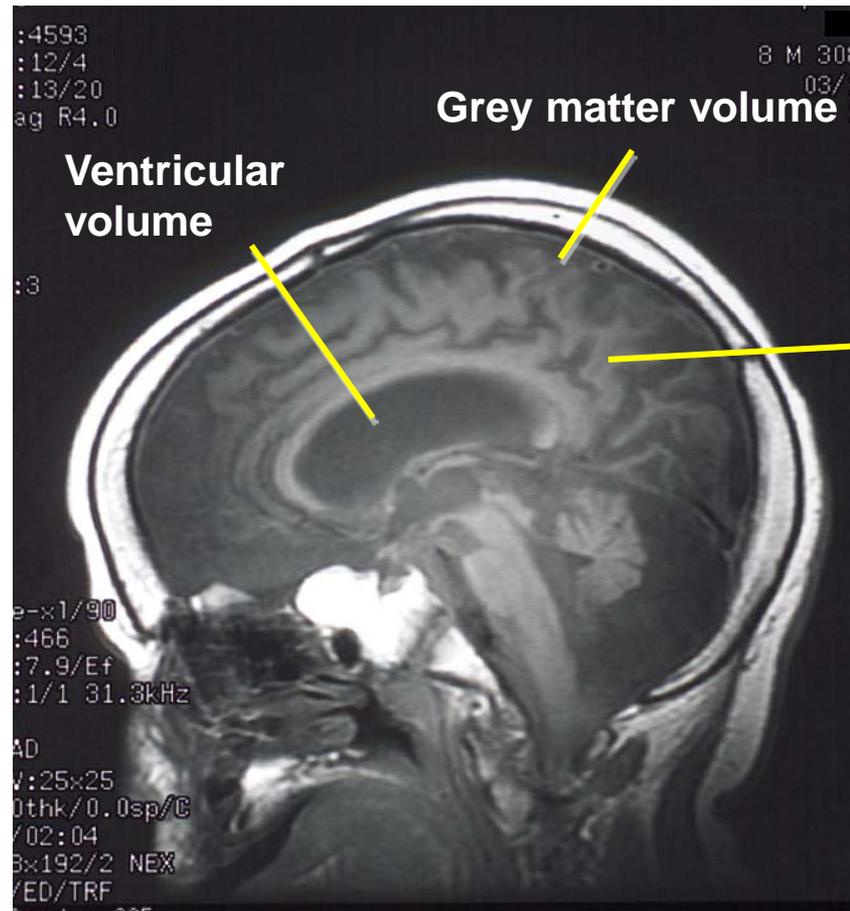
D. Receptive language



Child Health Questionnaire

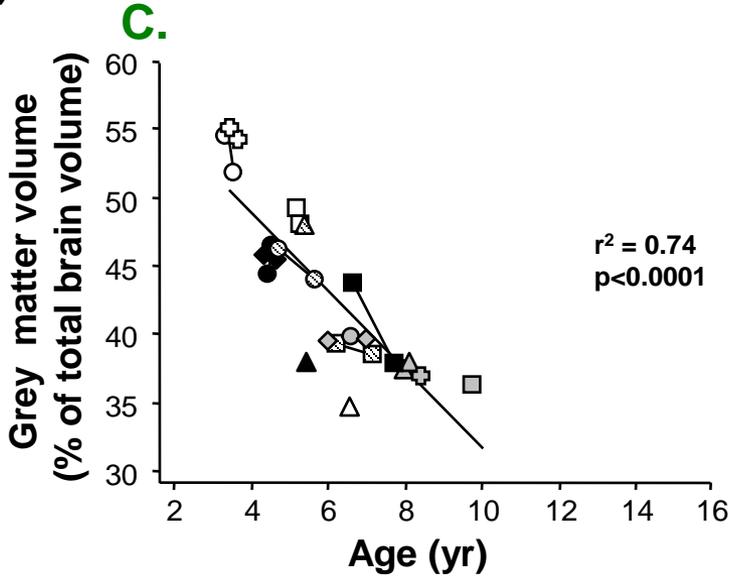
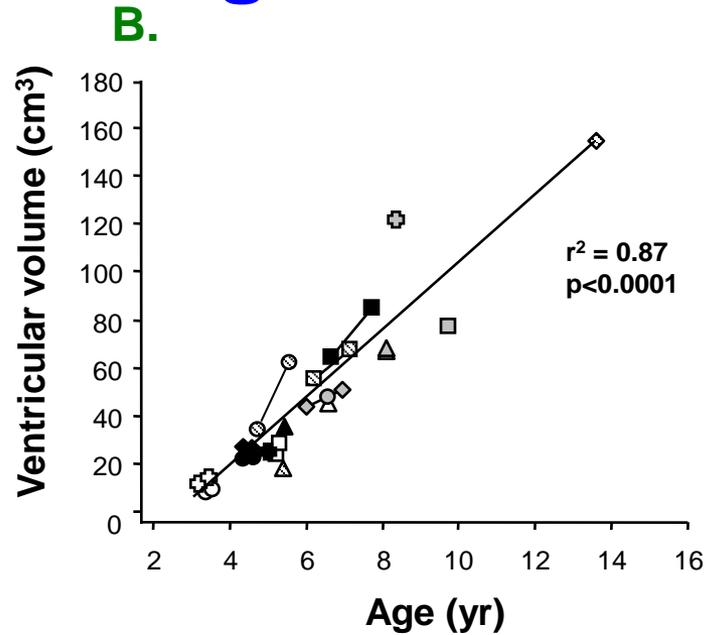
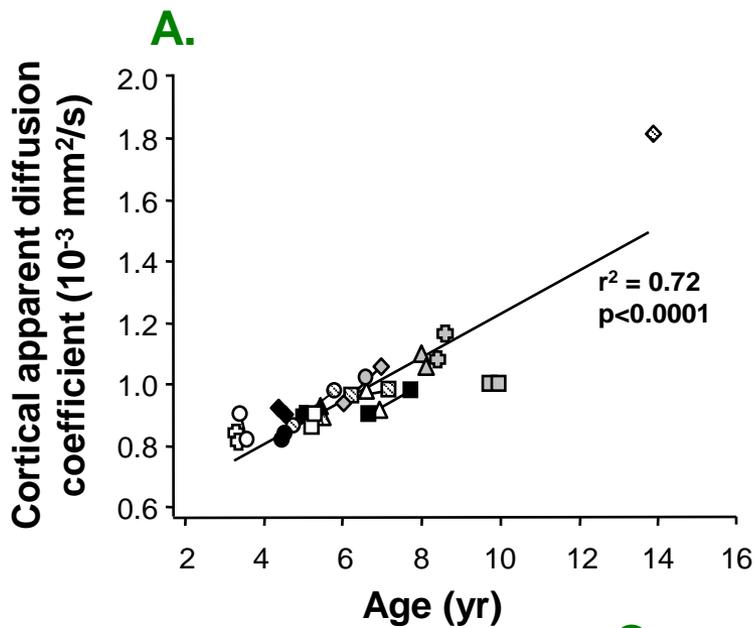


Quantitative MRI Parameters

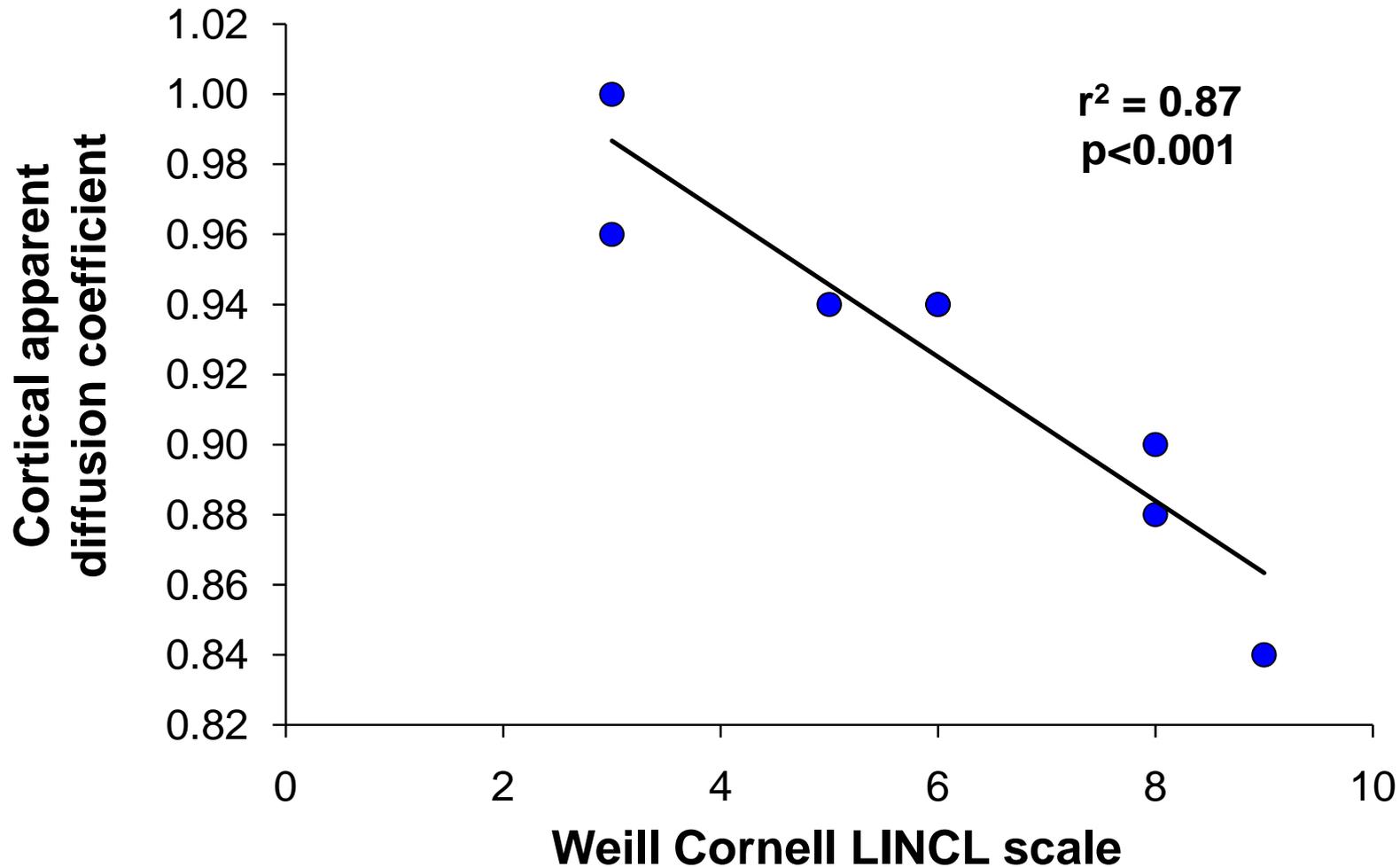


Cortical
apparent
diffusion
coefficient

Quantification of MRI Parameters in LINCL as a Function of Age



Cortical Apparent Diffusion Coefficient in LINCL as a Function of Disease Severity

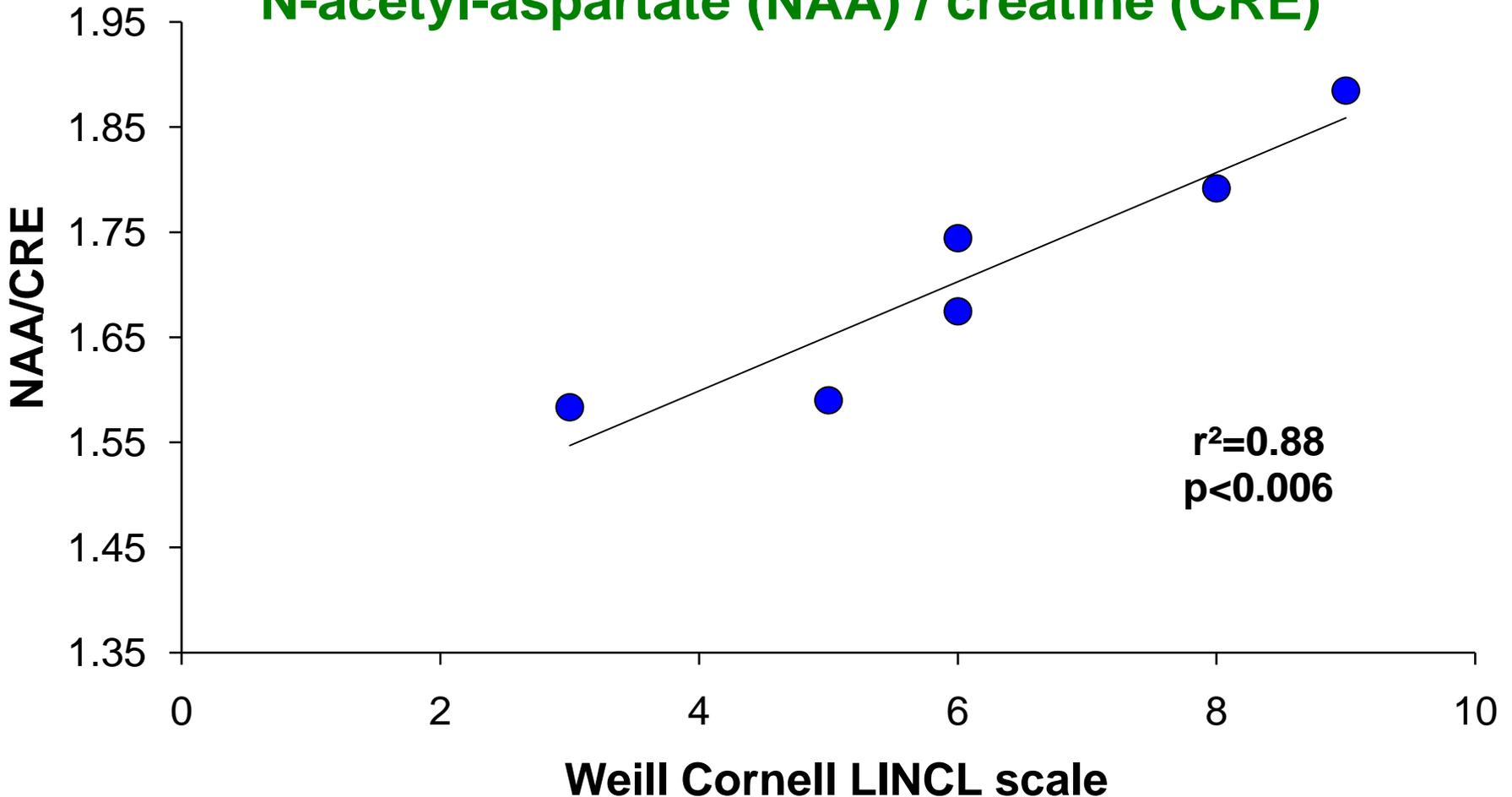


New NMR Assessments in LINCL

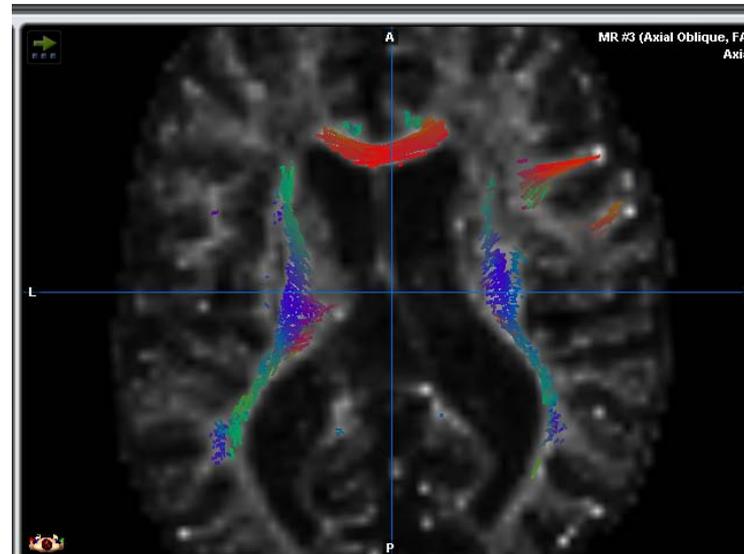
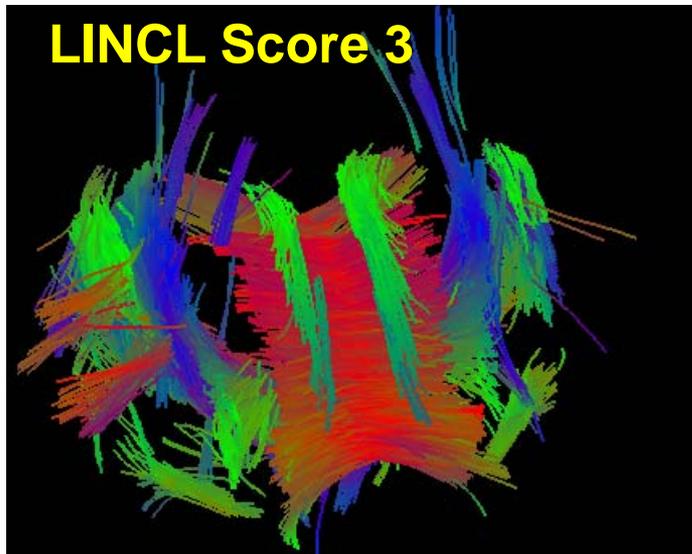
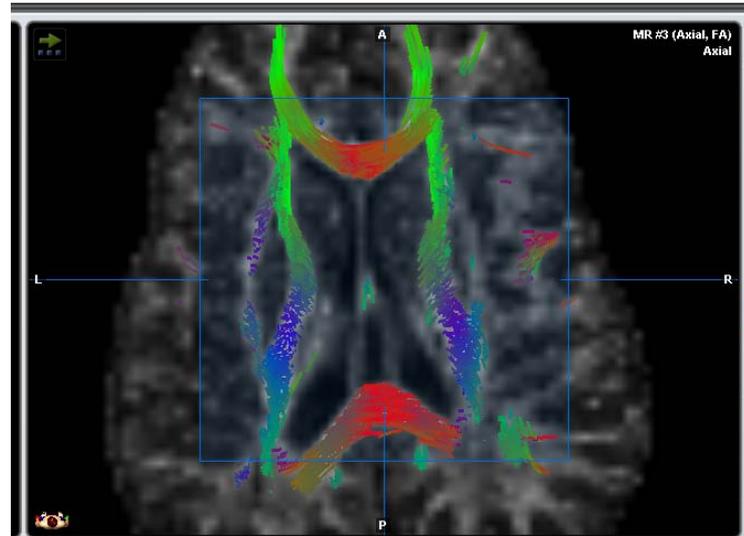
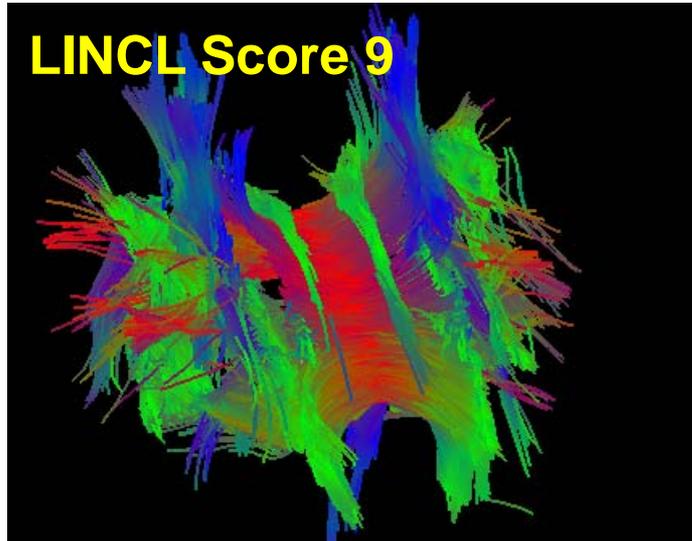
- Magnetic resonance spectroscopy
- Diffusion tensor imaging

Magnetic Resonance Spectroscopy in LINCL

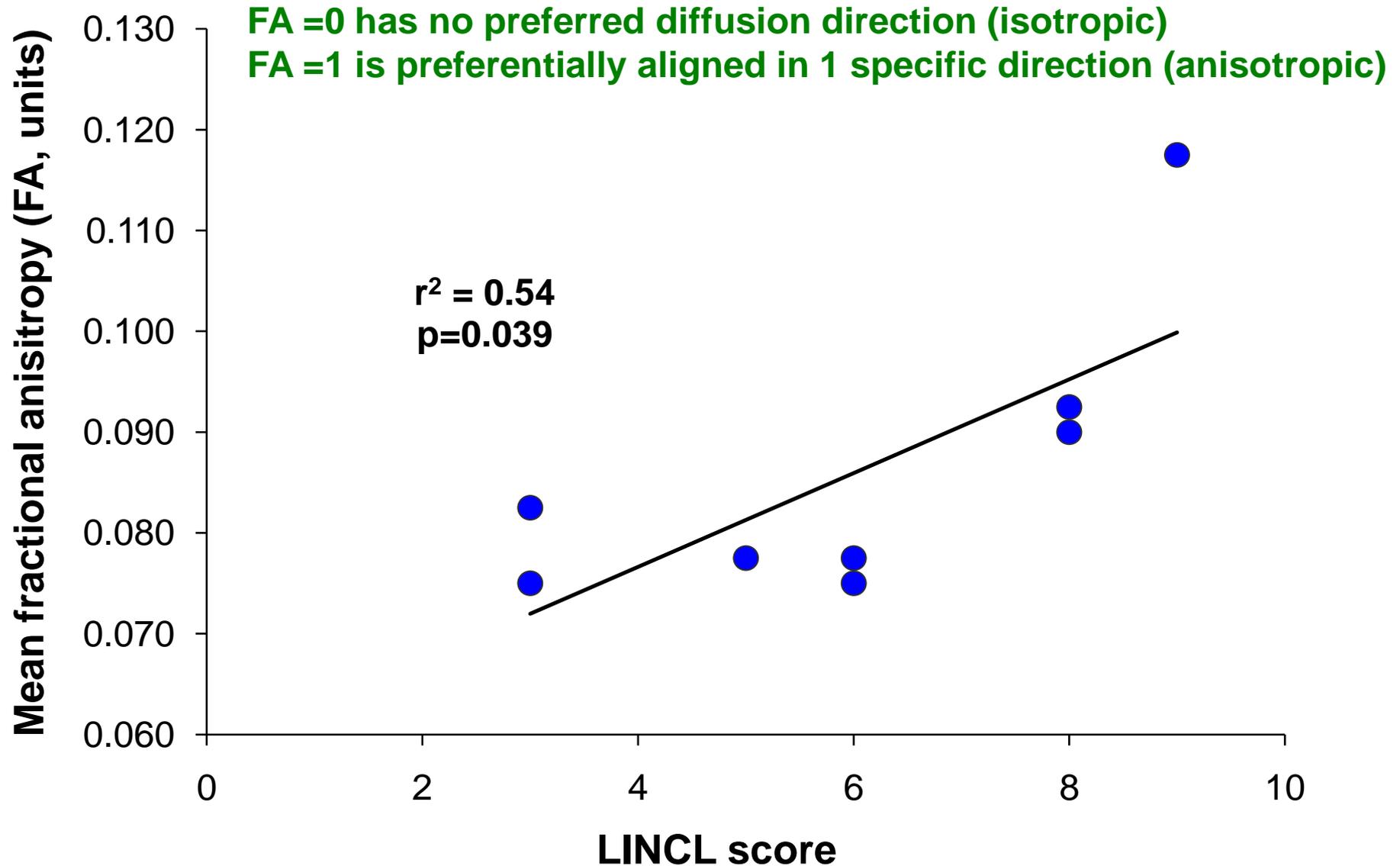
Whole brain peak area ratio
N-acetyl-aspartate (NAA) / creatine (CRE)



LINCL Diffusion Tensor Imaging – White Matter Tractography



LINCL Whole Brain Diffusion Tensor Imaging



Critical Need – To Develop Quantitative Phenotypes to Assess Efficacy

Clinical scales

- Quantitative clinical scales are, at best, crude, integrated measures of overall CNS function
- Even with multiple, blinded observers assessing videotapes, there is significant variability

Quantitative MRI

- Evolving methodology

Development of CSF Biomarkers for LINCL

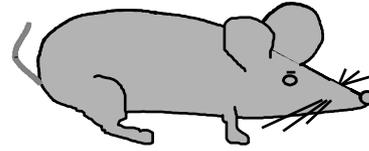
- Neurodegeneration-related
 - Tau/phospho-tau, neurofilaments, GFAP, tubulin
 - Lysosomal function – acid hydrolase, acid phosphatase, saponins, LAMP1,2
 - LINCL-specific – TPP1, mitochondrial ATPase subunit C, neuromedin, sulfated cholecystokinin-8
- Proteomics
- Metabolomics

Why Collect CSF Samples From the AAVrh.10 Trial When the Biomarker Methodology is Not Yet Established?

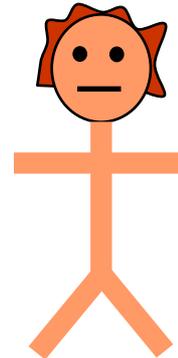
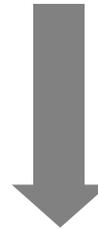
- Only ~200 children with LINCL worldwide
- Unique opportunity
 - Screening – data function of age, genotype, severity
 - Pre- and post-rx – efficacy data
- Archive samples until methods established

Development of CSF Biomarkers

- LINCL knockout mouse
- LINCL children function of age
- LINCL AAVrh.10 trial pre- and post-therapy (archive)



**LINCL
knockout
mice**



**Children
with LINCL**

Genetic Modification of the CNS

