

“NIH” Protocol
Direct CNS Administration of a
Replication Deficient Adeno-associated
Virus Gene Transfer Serotype rh.10
Expressing the Human CLN2 cDNA to
Children with Late Infantile Neuronal
Ceroid Lipofuscinosis
RAC #0904-977

R. Crystal
Weill Cornell Medical College

3-8-12

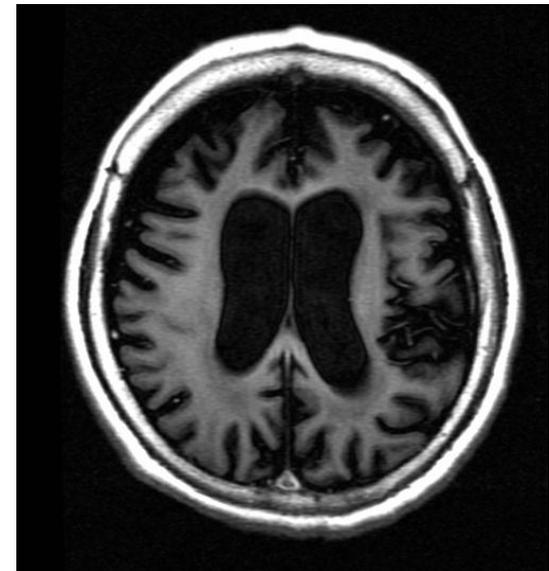
“Parallel” Protocol

**Phase I/II Study: Direct CNS Administration of
a Replication Deficient Adeno-associated
Virus Gene Transfer Vector Serotype rh.10
Expressing the Human CLN2 cDNA to
Children with Late Infantile Neuronal Ceroid
Lipofuscinosis with Uncommon Genotypes
and/or Moderate to Severe Impairment**

RAC #1008-1064

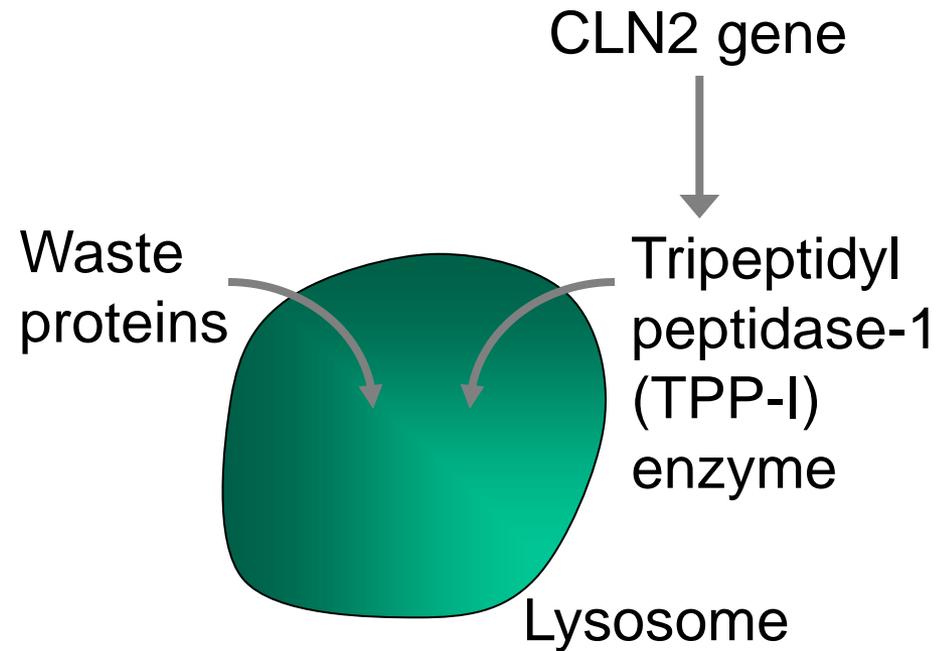
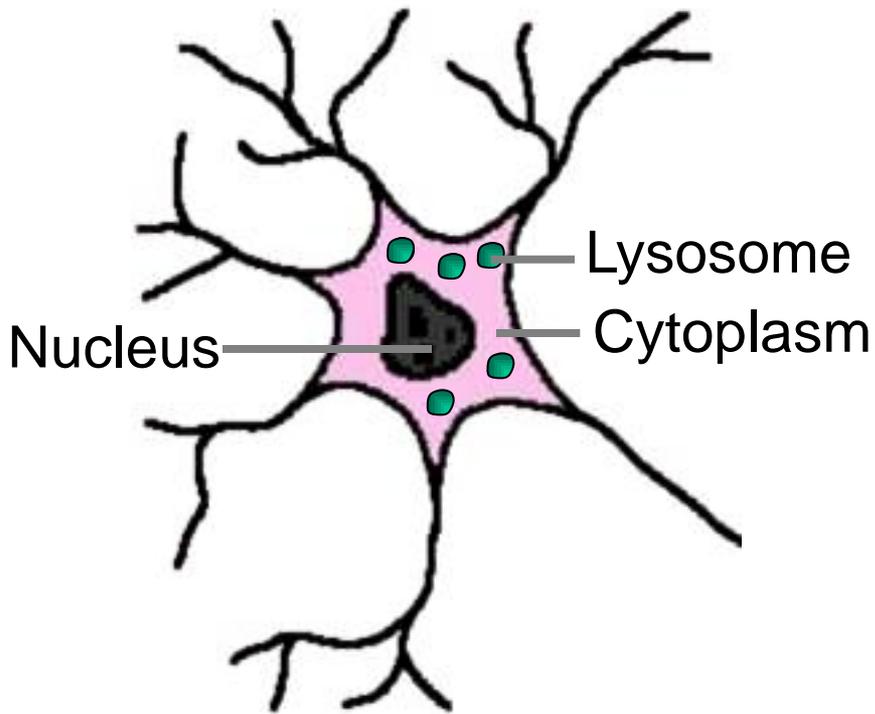
Late Infantile Neuronal Ceroid Lipofuscinoses (LINCL, Batten Disease)

- Autosomal recessive, ~ 400-600 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



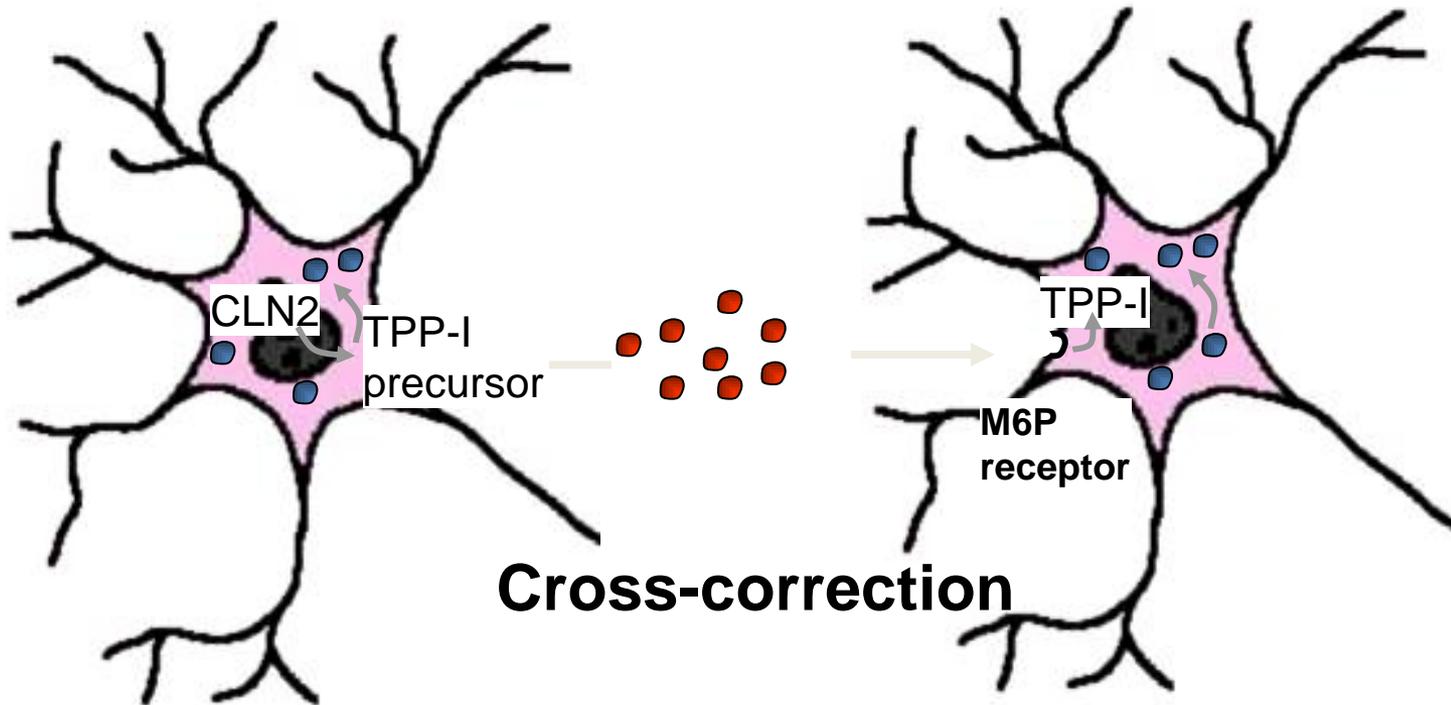
LINCL Is Caused by Mutations in the CLN2 Gene

Neuron

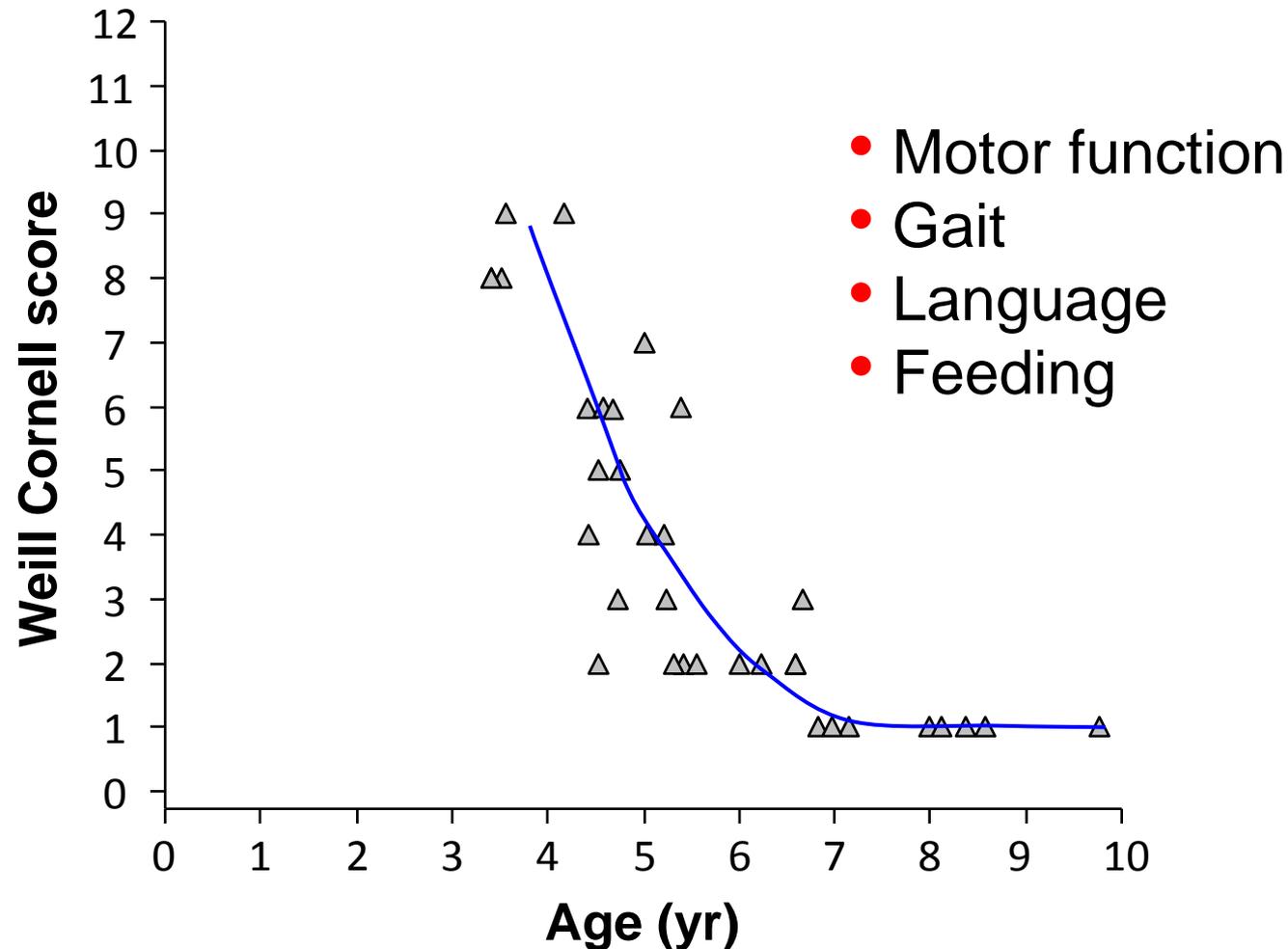


Cross-correction of CNS Cells via the Mannose-6-phosphate Pathway

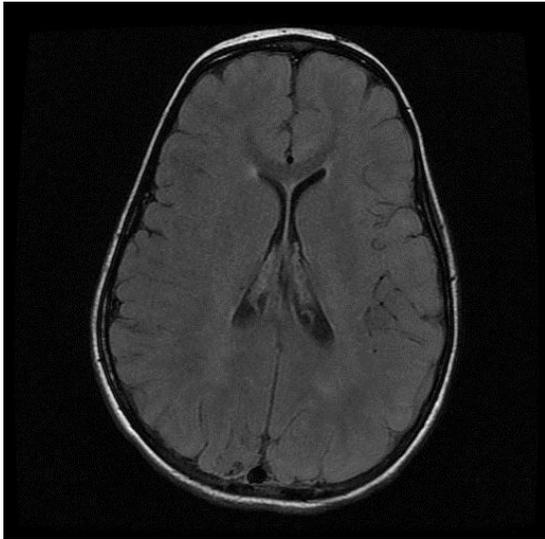
Neuron



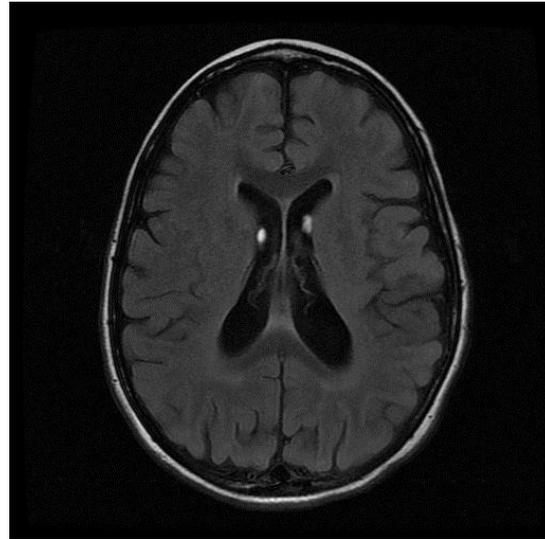
LINCL Age-dependent Changes in the Weill Cornell LINCL Score



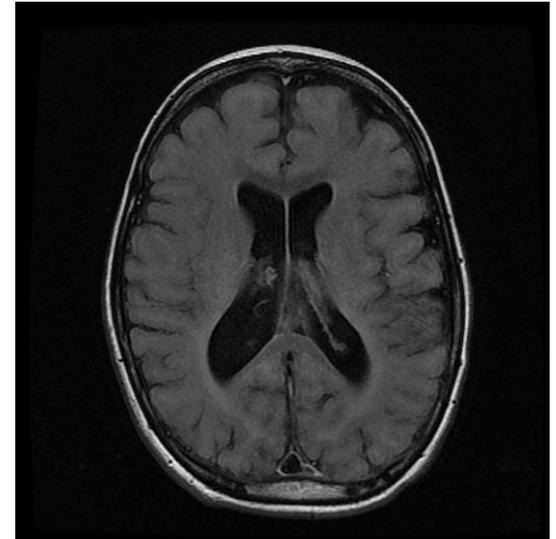
CNS MRI Imaging LINCL



LINCL 9

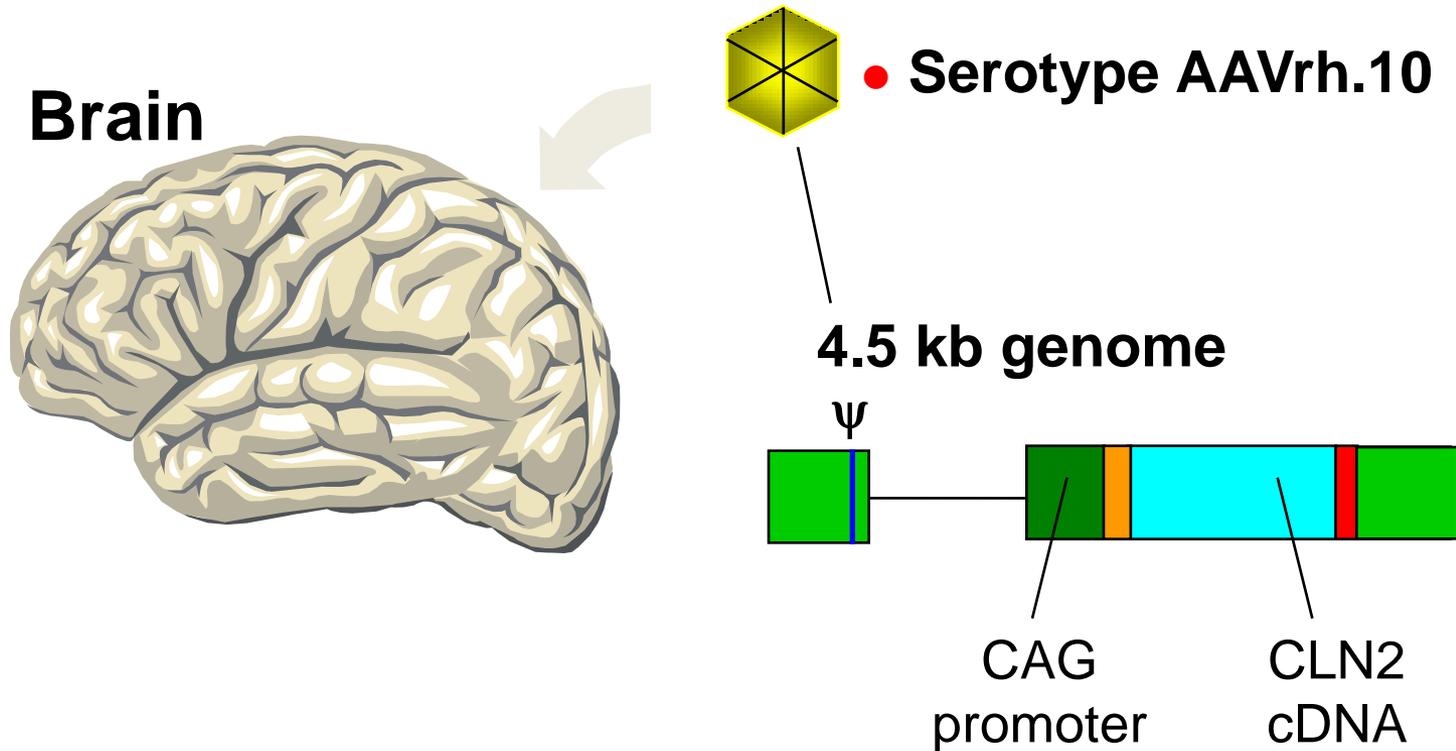


LINCL 6



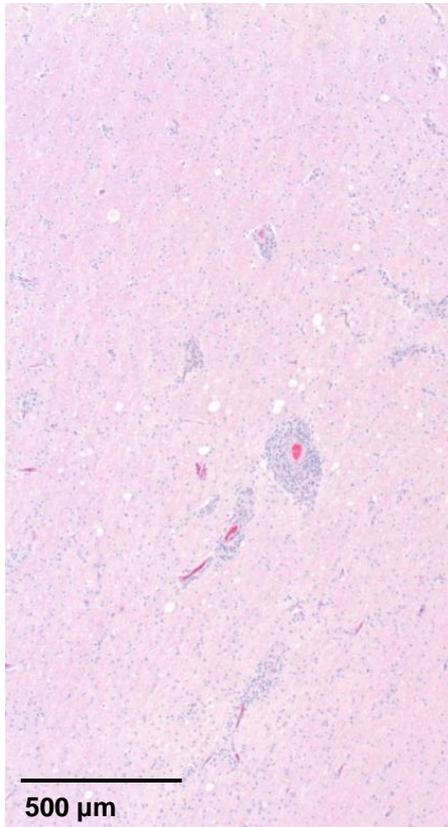
LINCL 3

2nd Generation Gene Therapy for LINCL

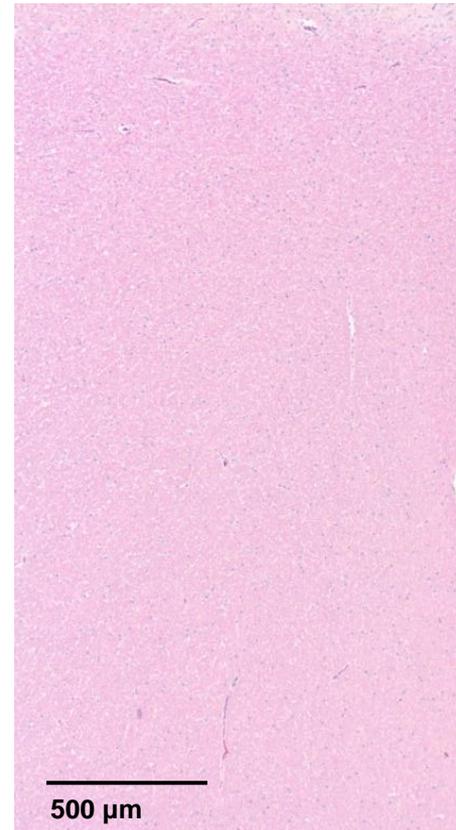


Toxicology Assessment of AAVrh.10hCLN2 Administration to Non-human Primate CNS

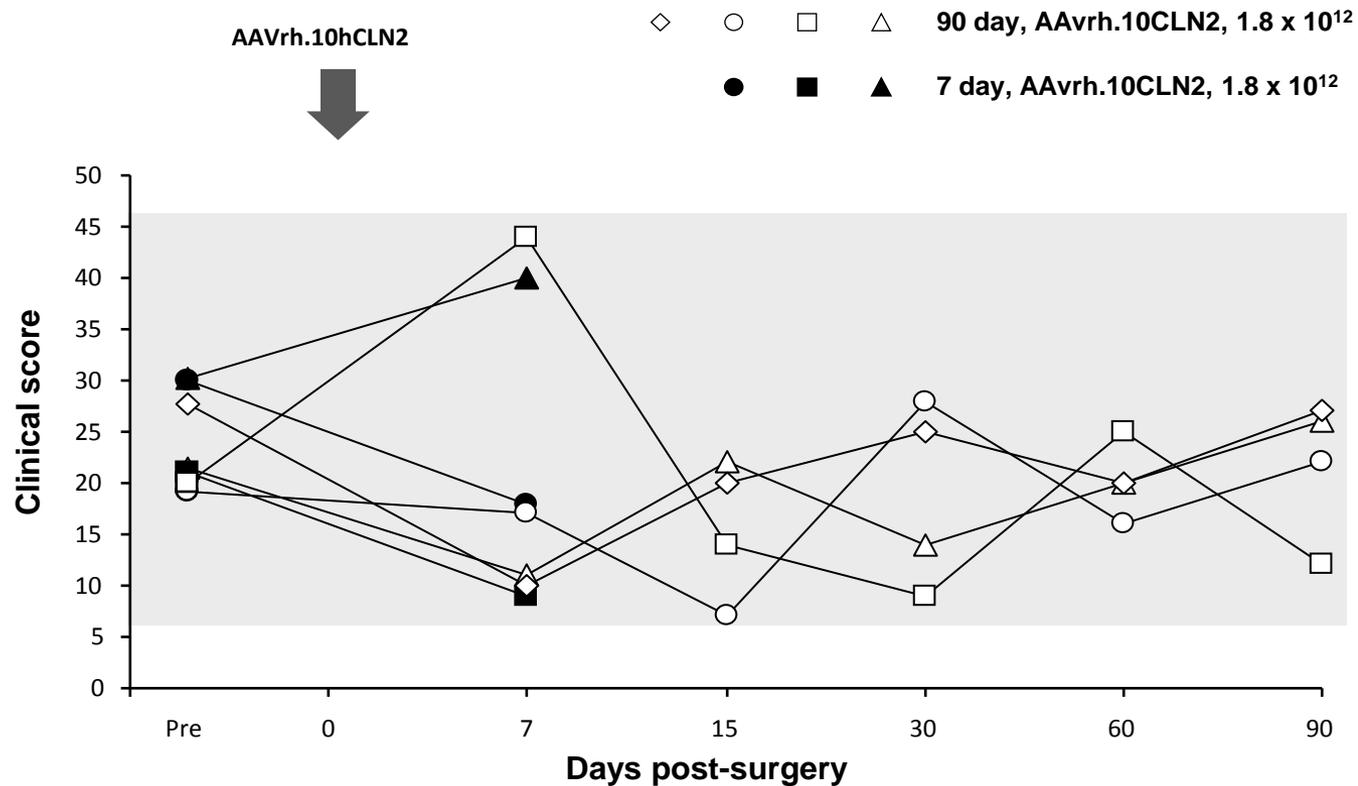
**At the administration site
3 months**



**Distant from the administration site
3 months**



Effect of AAVrh.10hCLN2 CNS Administration on Behavior of Non-human Primates



Overall NIH Trial Design

Subject with LINCL

Screening protocol
(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
LINCL mild-moderate

Outcome Measures

Primary

- Weill Cornell LINCL score¹
- Quantitative MRI

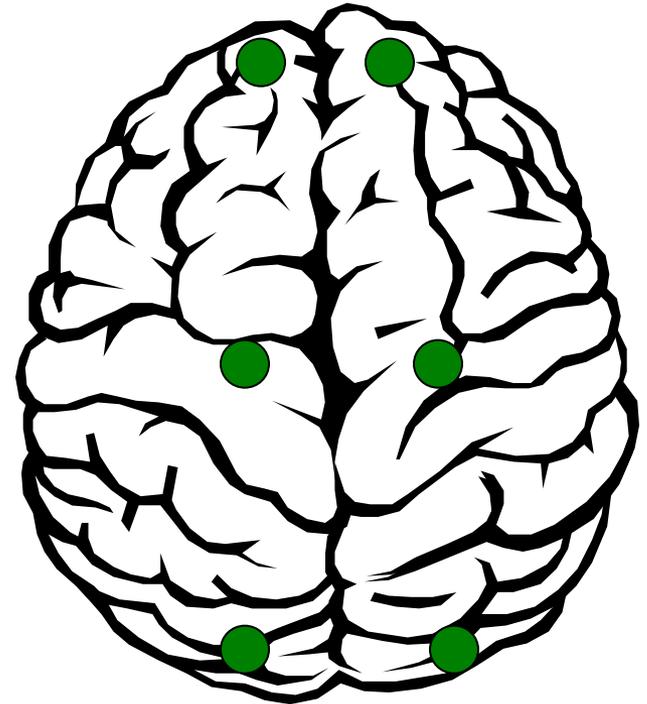
Secondary

- Mullen score
- CHQ Quality of Life questionnaire

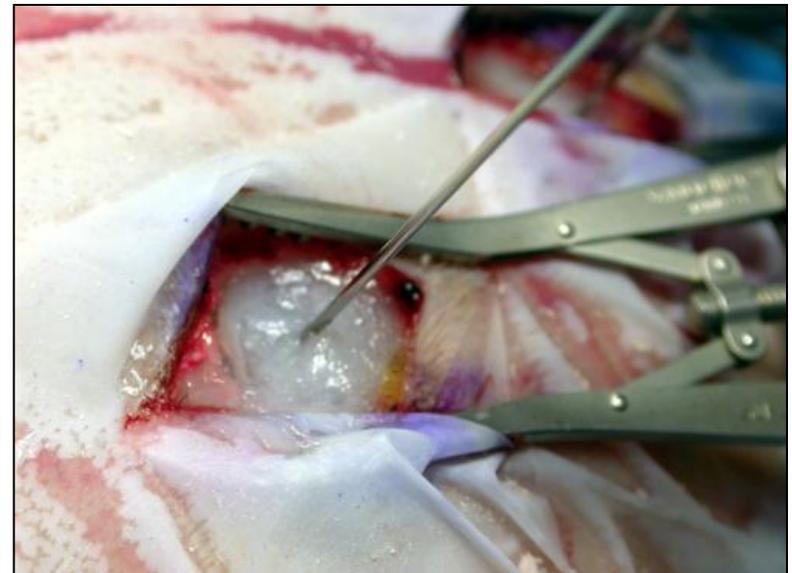
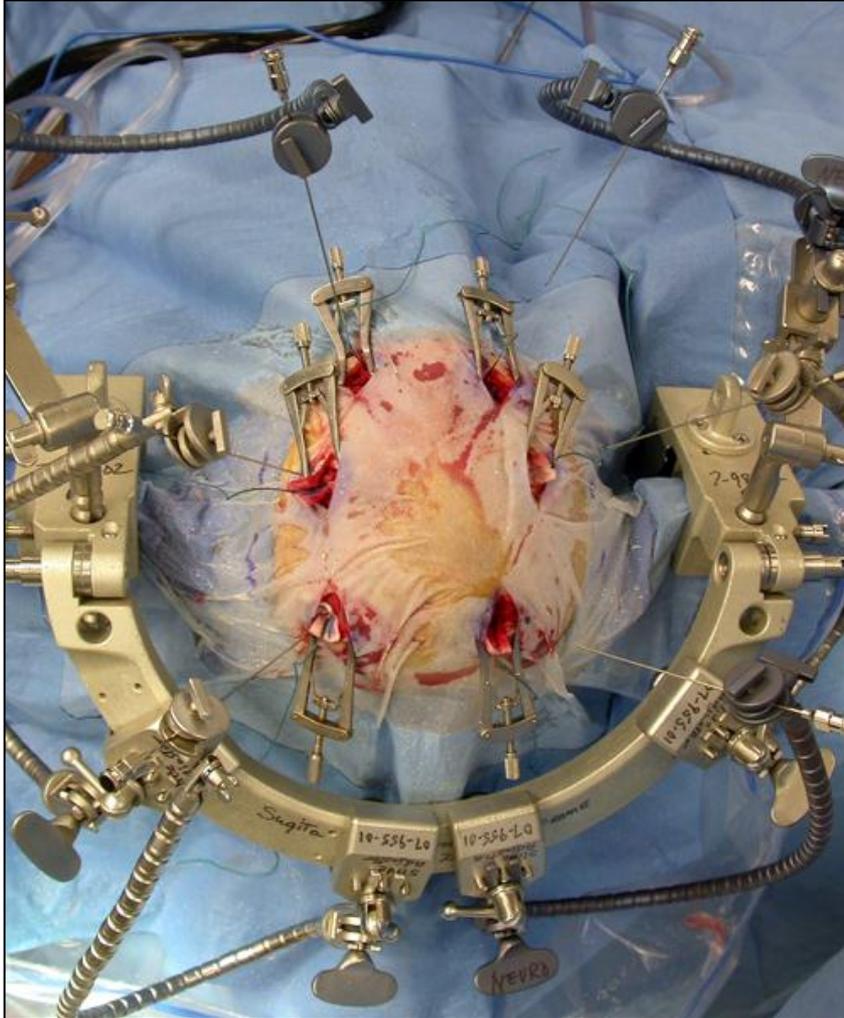
¹ Video, blinded assessment by 3 independent pediatric neurologists

Vector Administration

- 6 burr holes
- Administration at 2 sites (different levels) per burr hole
- 2 $\mu\text{l}/\text{min}$ to minimize damage, 300 $\mu\text{l}/\text{burr hole}$ (150 μl at each of 2 sites)



AAV Vector CNS Administration



Status of the AAVrh.10 Trial

Screening Protocol

- n=26 have undergone initial screening evaluations
- 9 male, 17 female
- ages 2y 7m–8y 1m
- range of 1–11 on LINCL scale

Vector Protocol (“NIH”)

- n=7
- 4 male, 3 female
- ages 3y 6m–7y 3m
- 6 evaluated at 6 ms; 2 evaluated at 12 ms

Vector Protocol (“Parallel”)

- n=3
- 1 male, 2 female
- ages 5y 11m–8y 4 m
- 1st subject withdrew before month 6 visit; 2nd subject will reach month 6 follow up April 2012

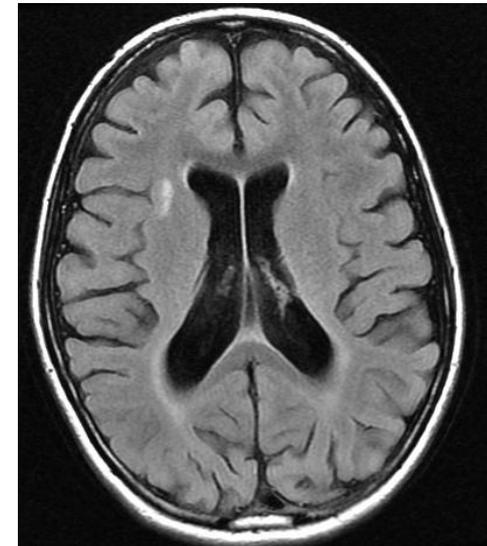
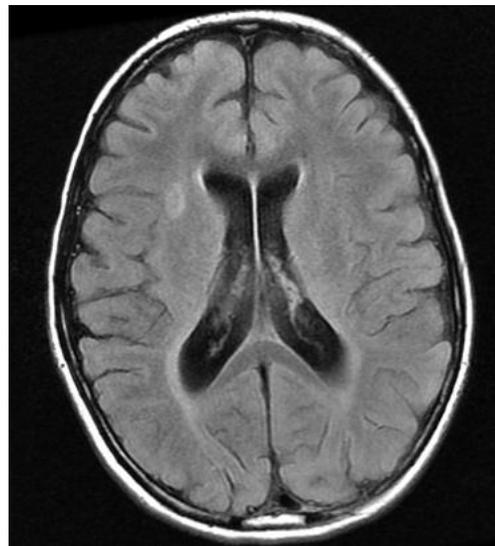
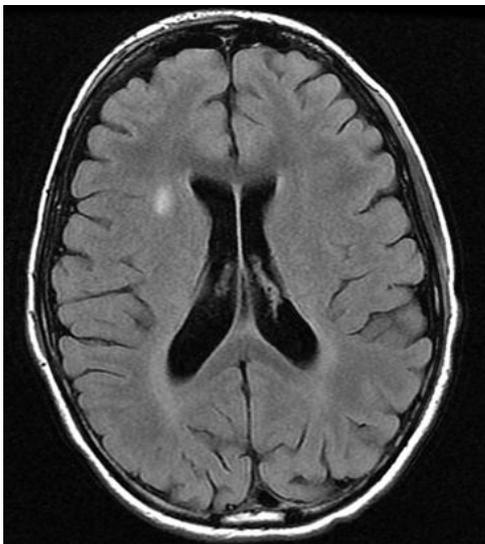
T2 FLAIR with Diffusion Restriction

Post-op 1 day

Month 6

Month 12

**Subject A-
BDrh-03**

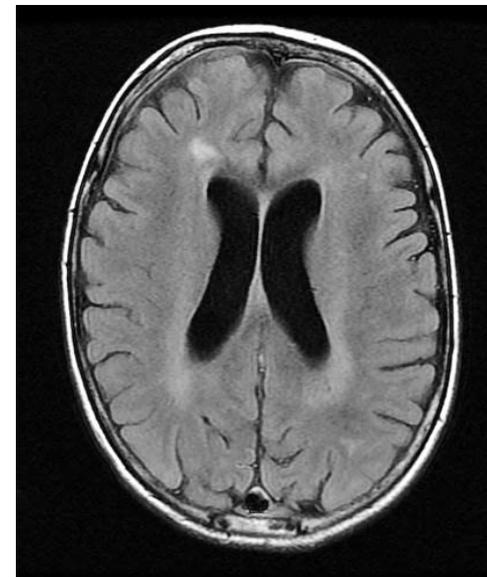
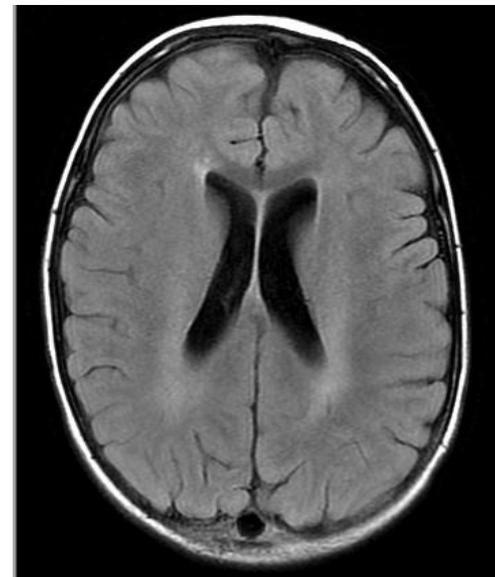
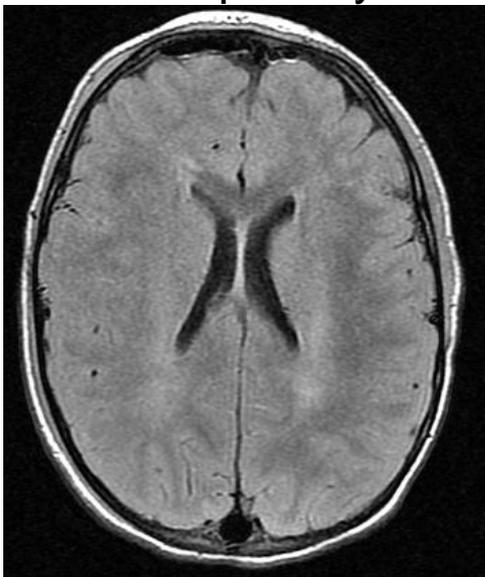


Post-op 1 day

Month 6

Month 12

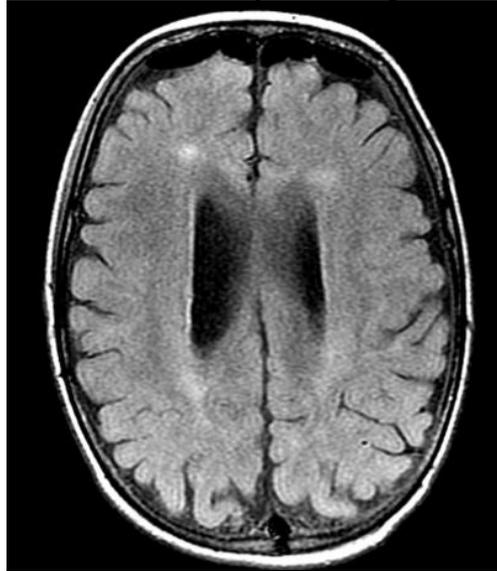
**Subject B-
BDrh-12**



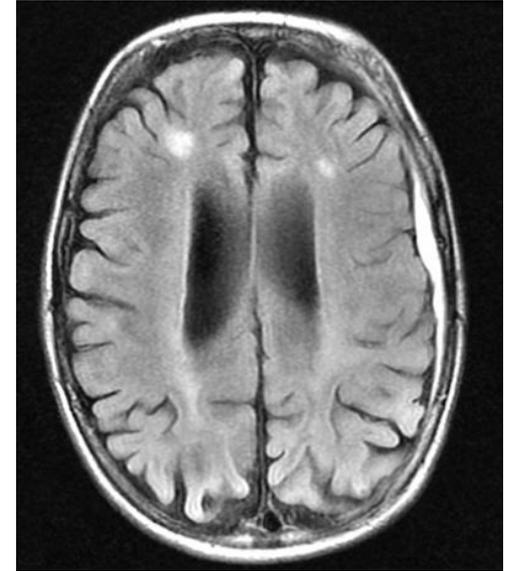
T2 FLAIR with Diffusion Restriction (2)

Subject D- BDrh-14

Post-op 1 day

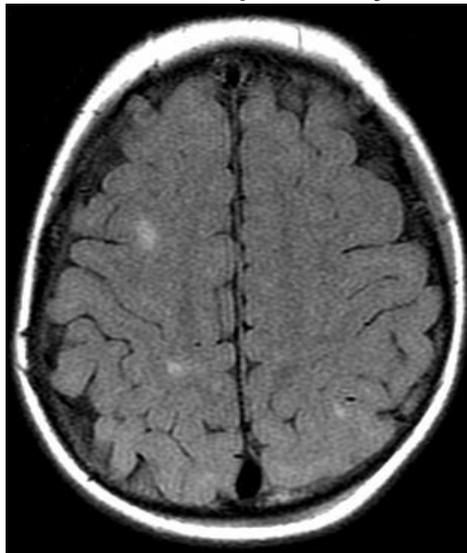


Month 6

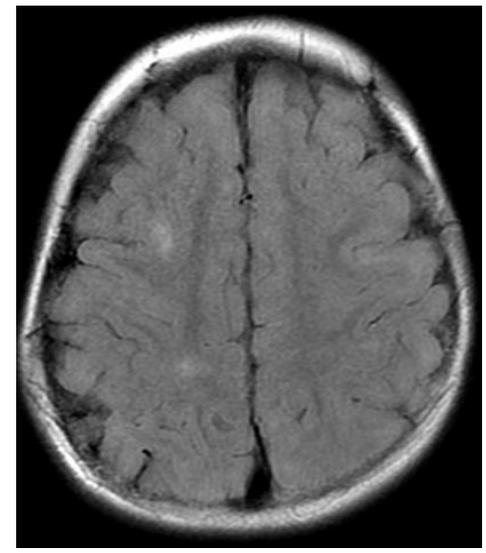


Subject E- BDrh-15

Post-op 1 day

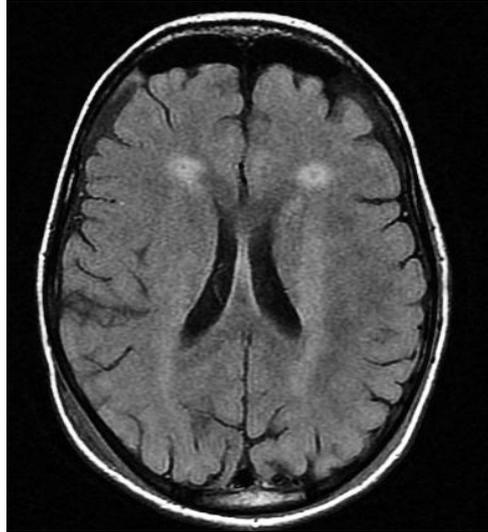


Month 6

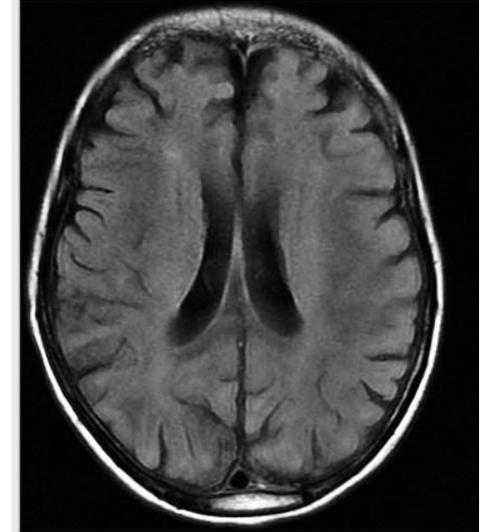


T2 FLAIR without Significant Diffusion Restriction

Post-op 1 day

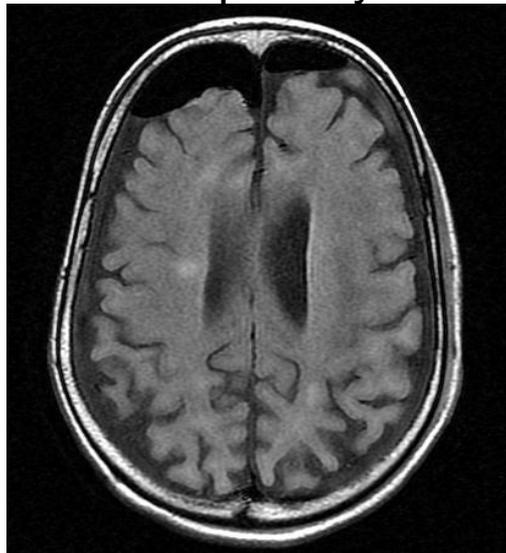


Month 6

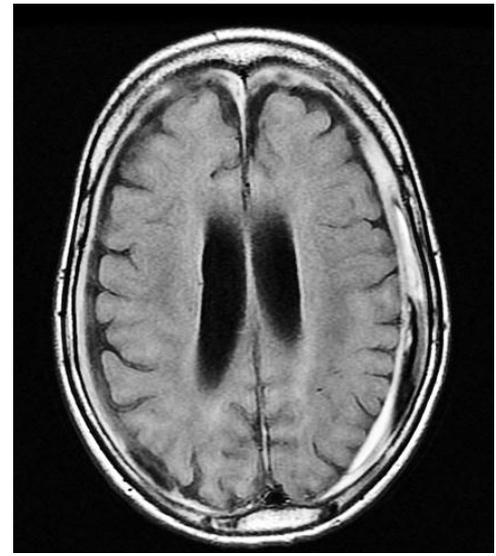


Subject C- BDrh-13

Post-op 1 day

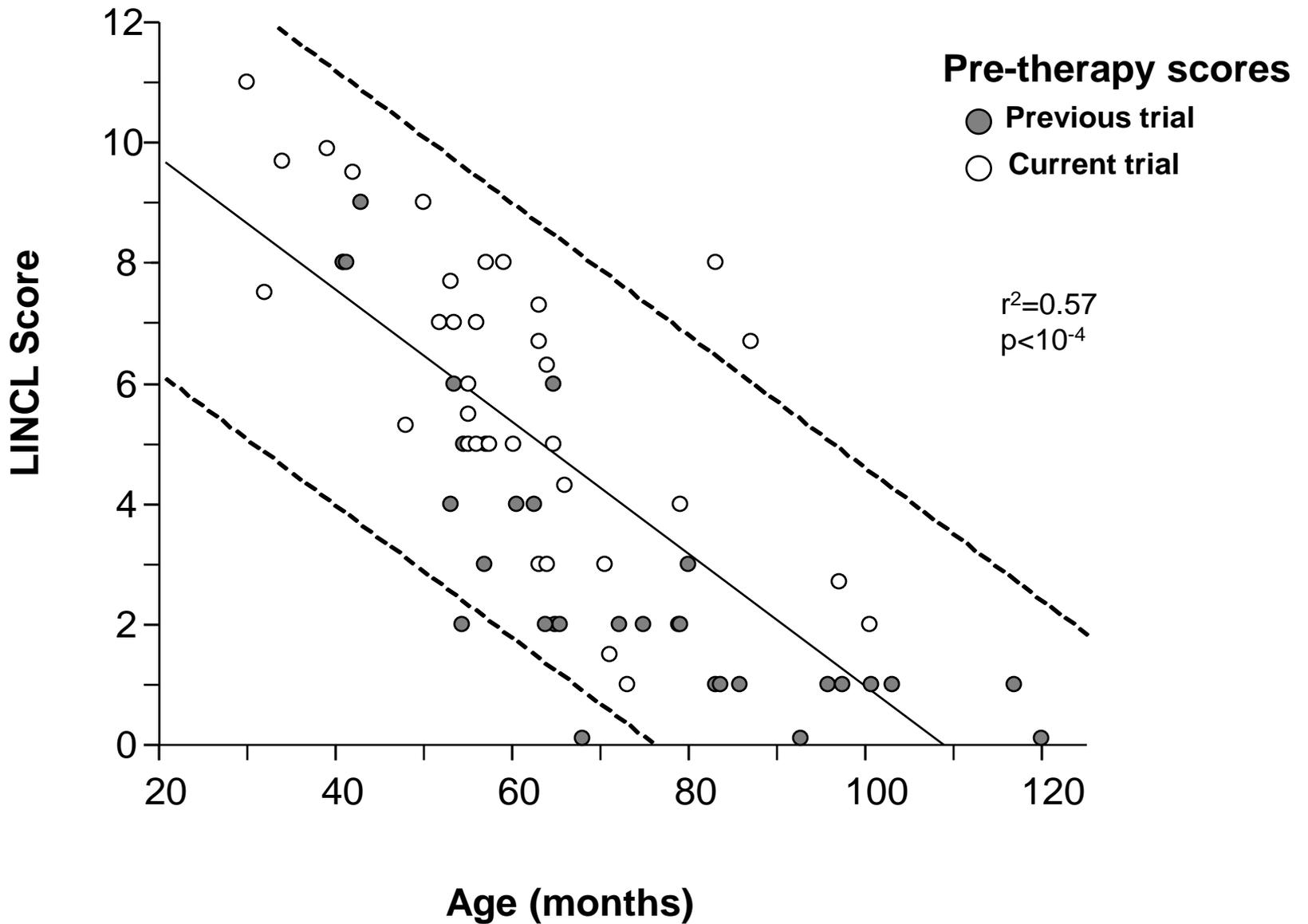


Month 6

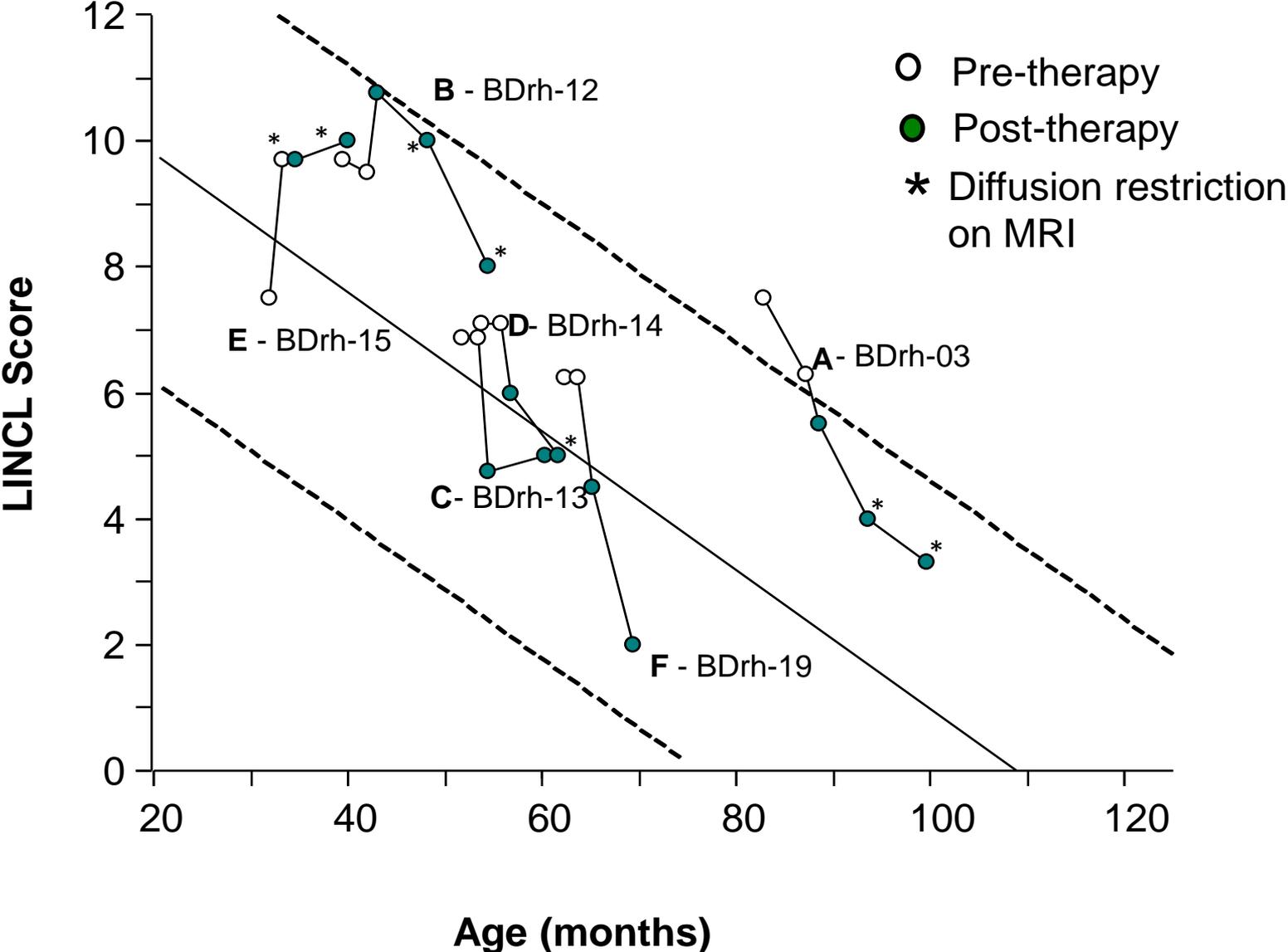


Subject F- BDrh-19

LINCL Score vs Age

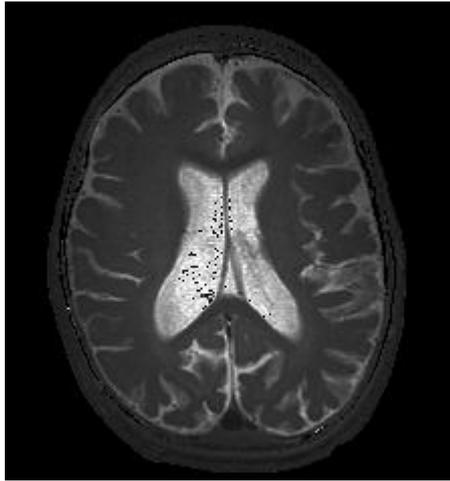


LINCL Score vs Age in Treated Subjects

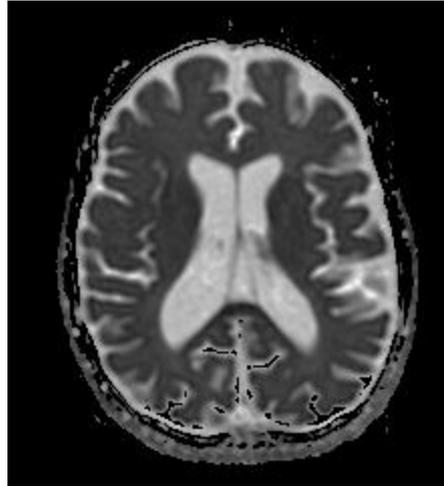


CNS MRI Quantitative Assessment

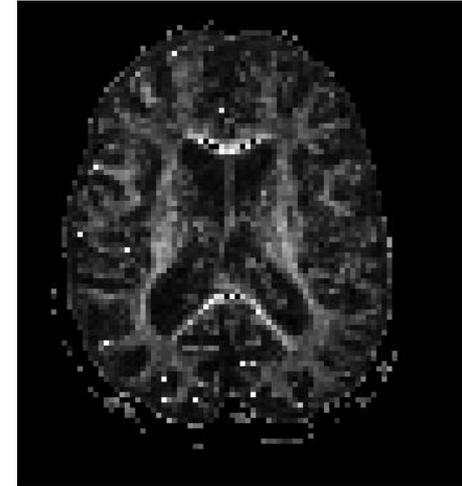
A. T_2



B. Apparent diffusion coefficient



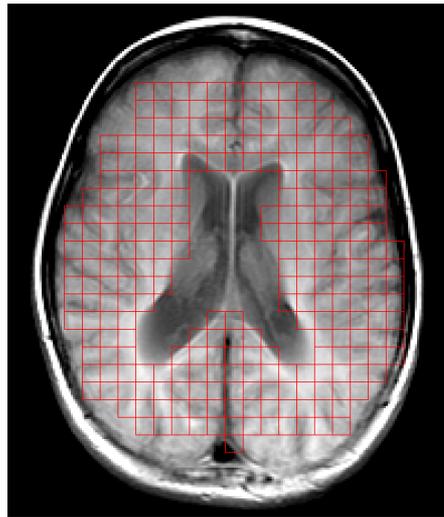
C. Fractional anisotropy



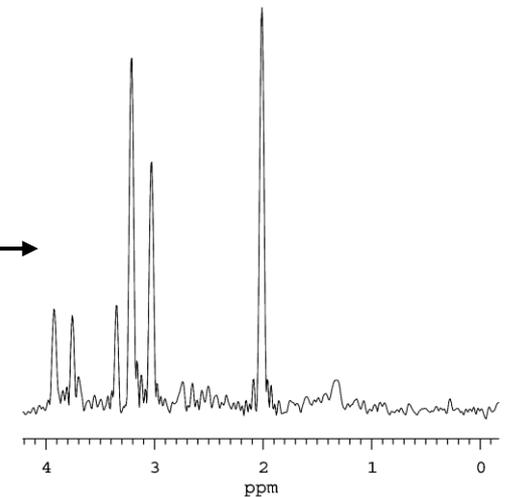
D. % CSF volume



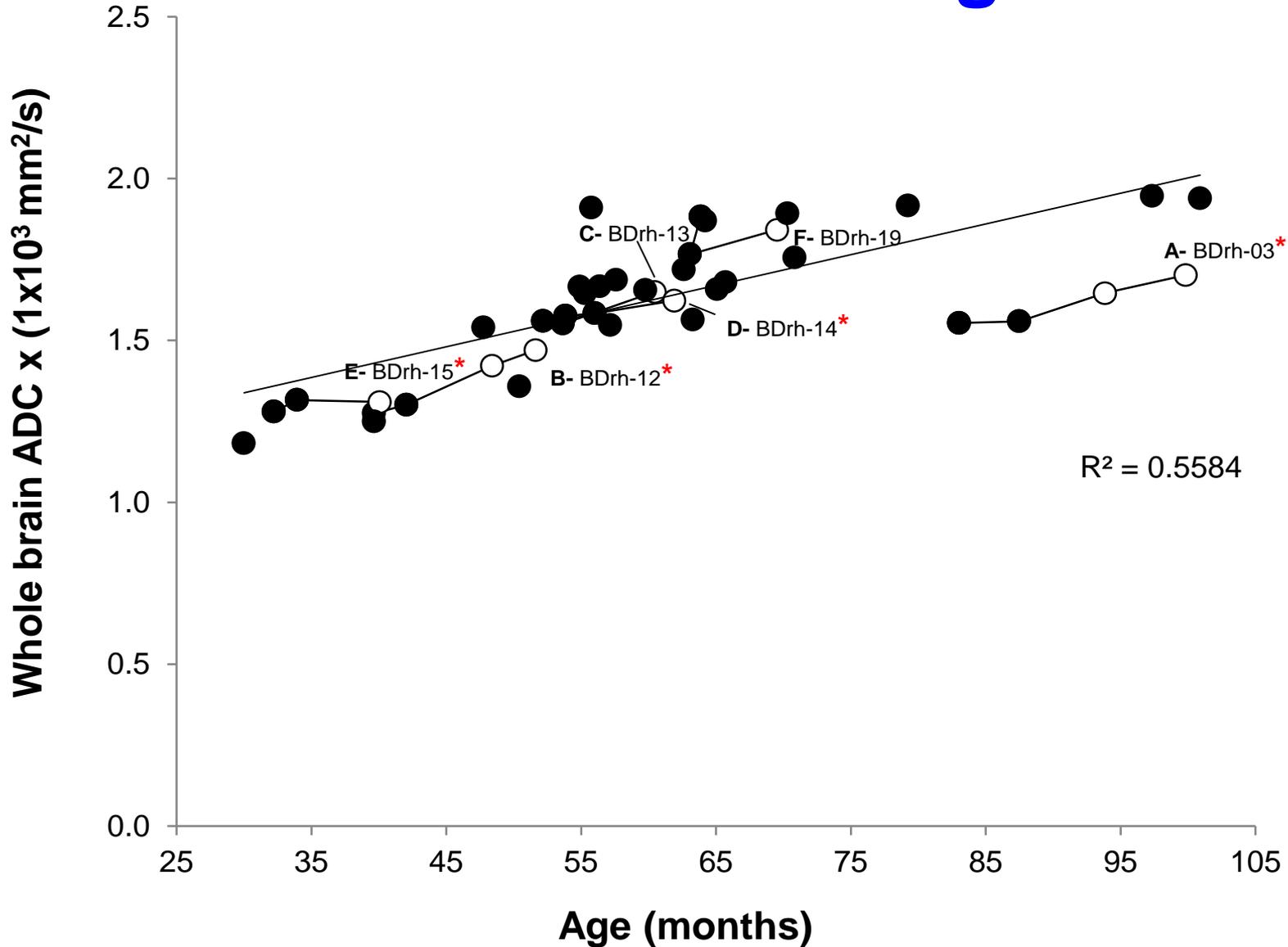
E. MRS



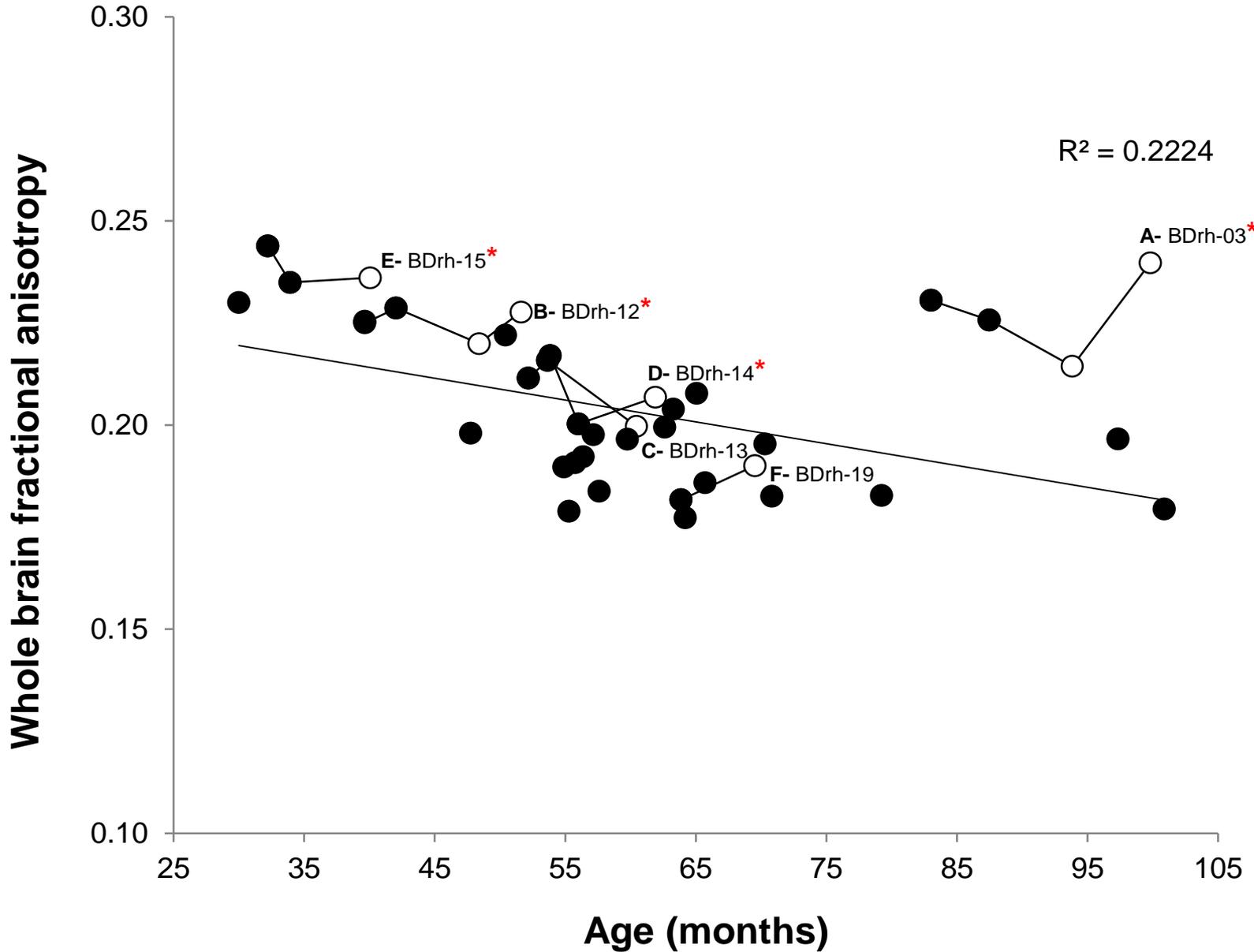
F. MRS spectrum



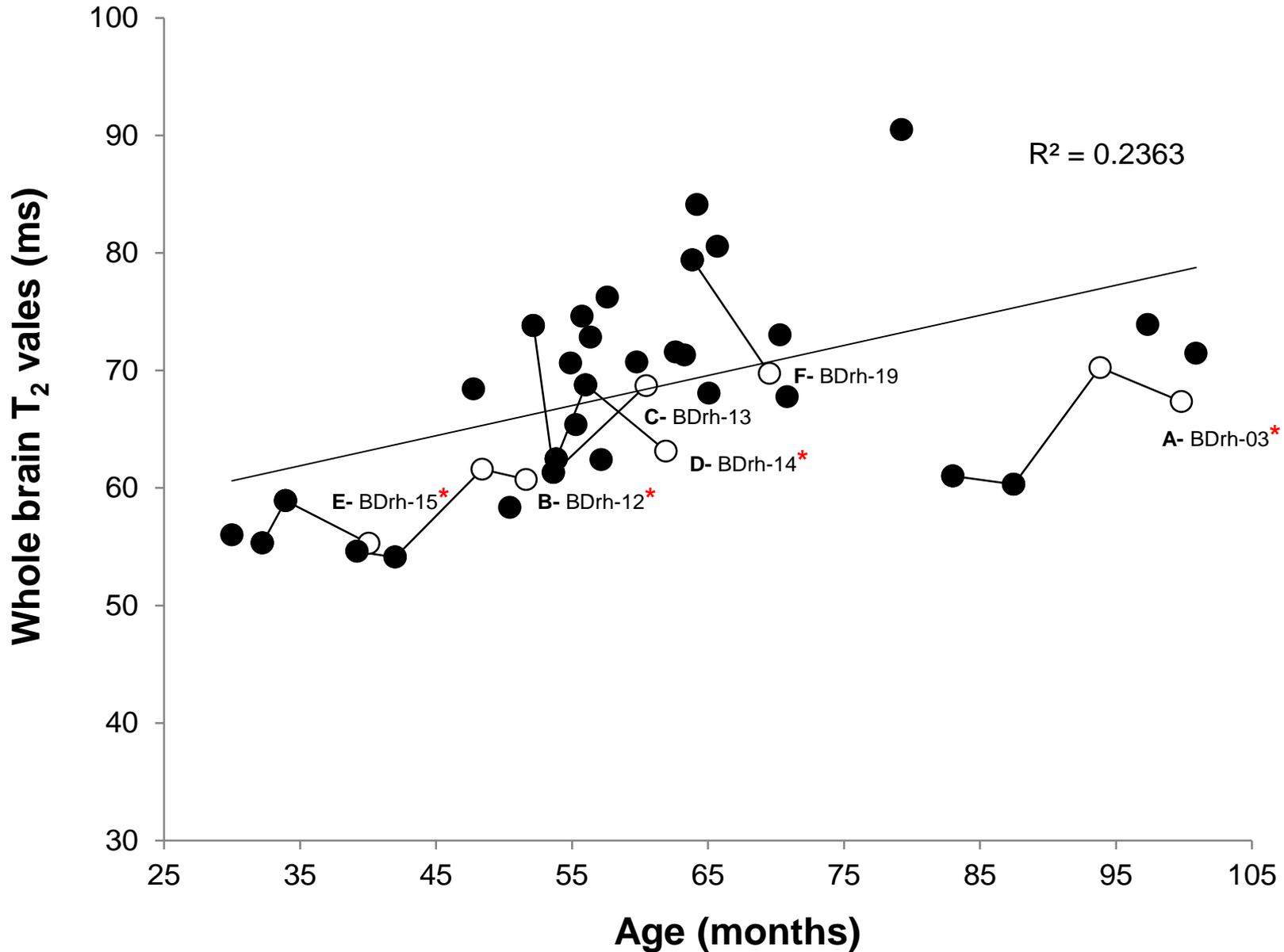
Whole Brain Apparent Diffusion Coefficient vs Age



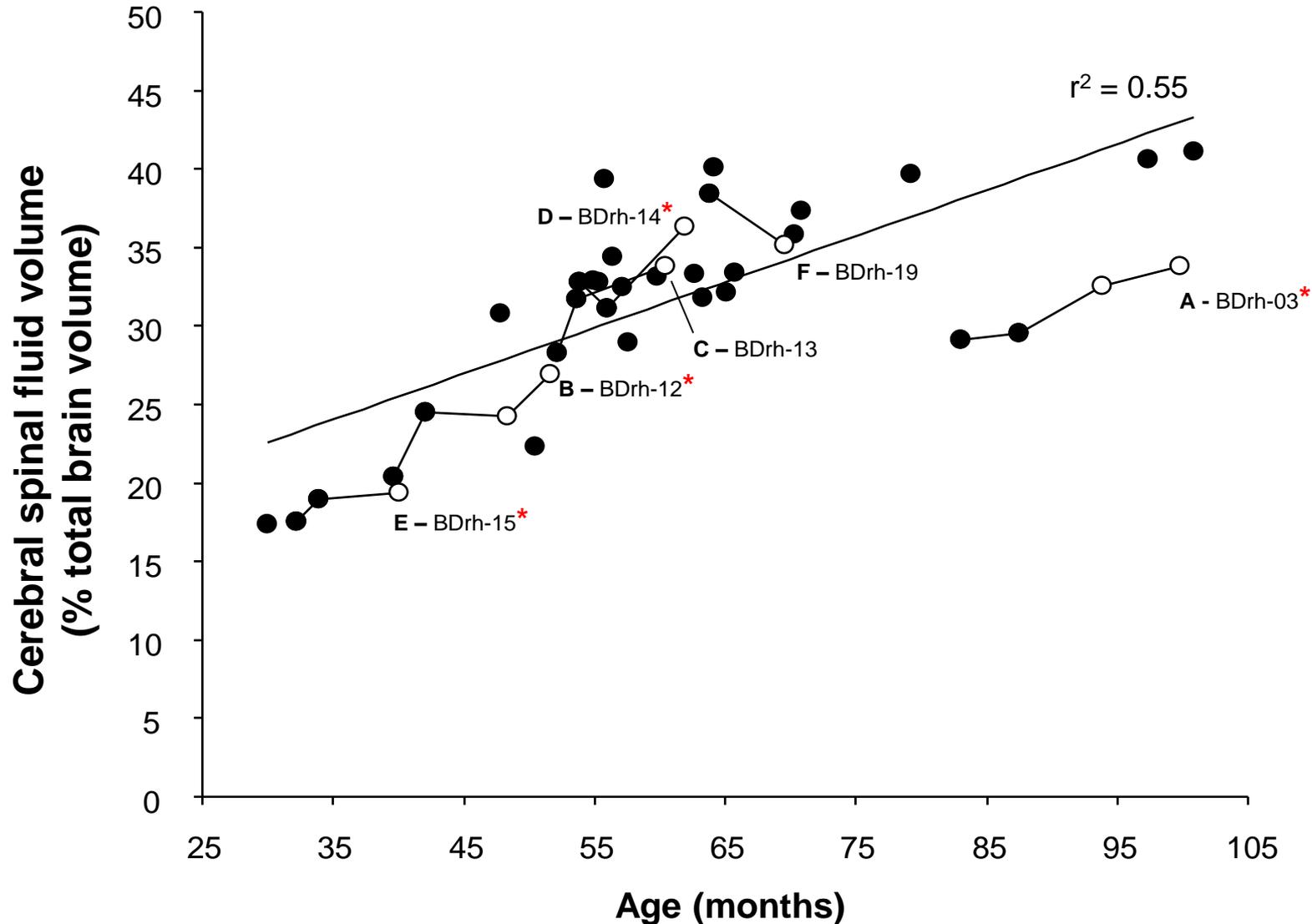
Whole Brain Fractional Anisotropy



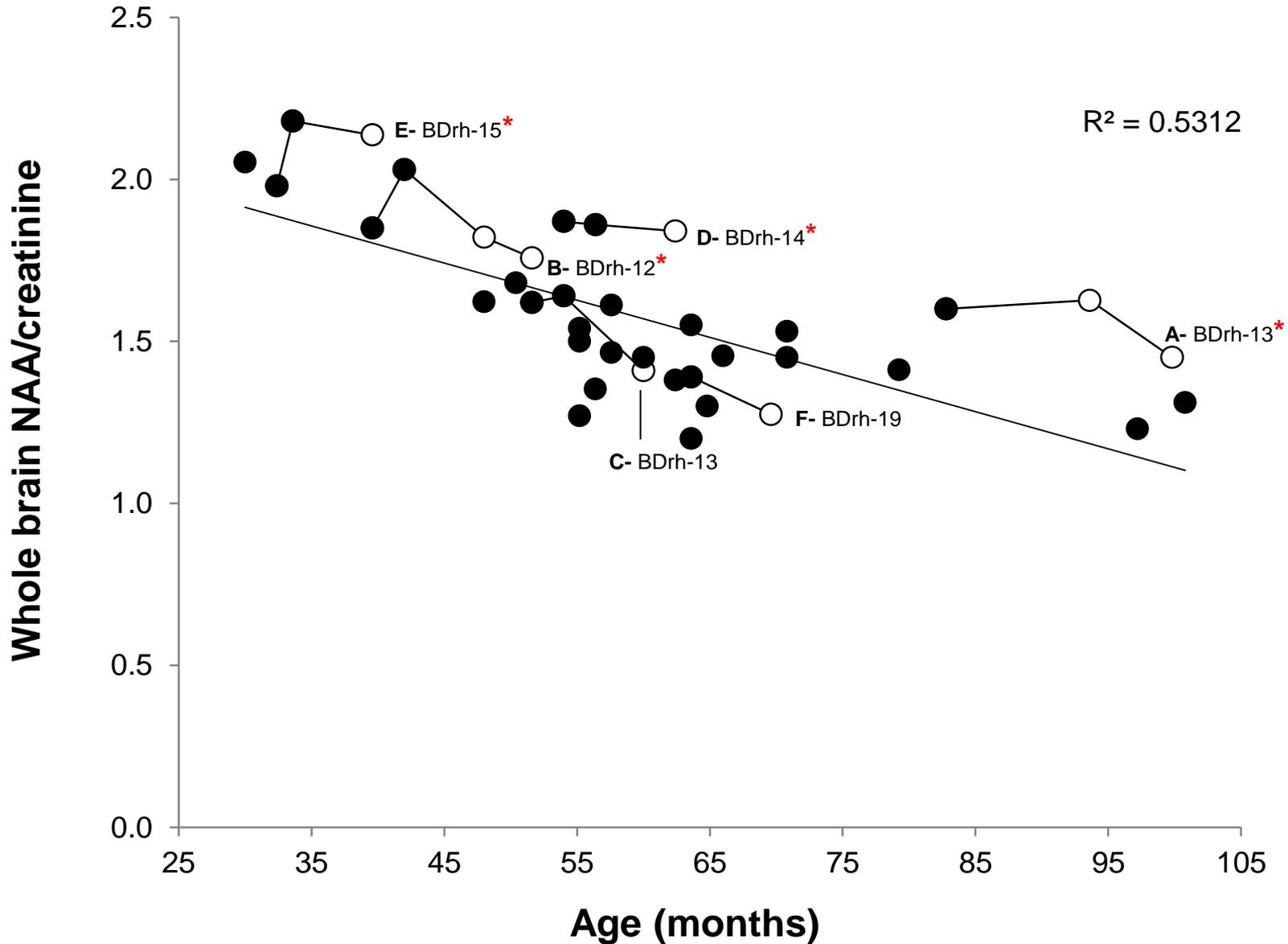
Whole Brain T₂ Values



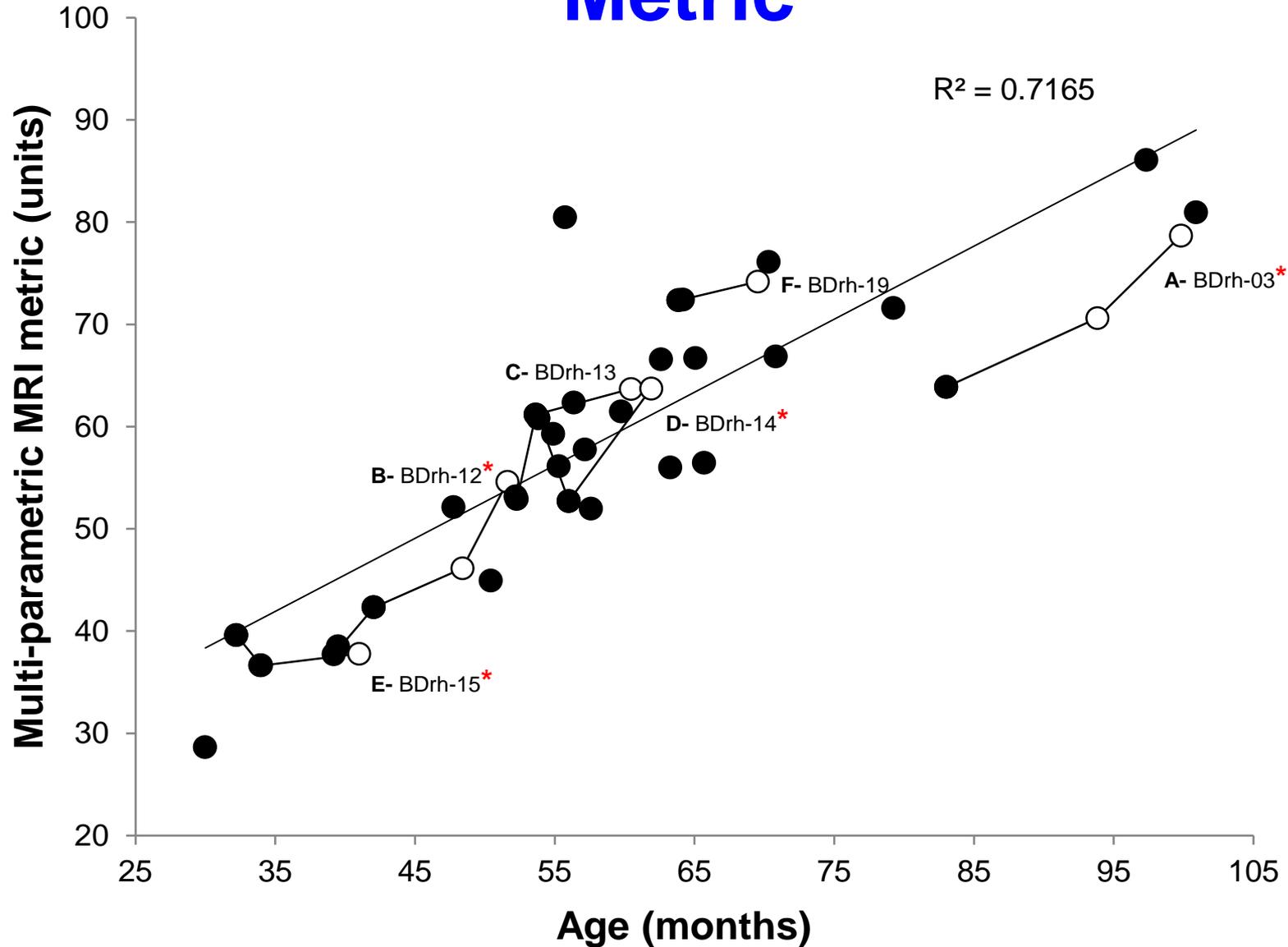
Cerebral Spinal Fluid Volume (% Total Brain Volume)



Whole Brain Spectroscopic Analysis



Multi-parametric MRI Multi-parameter Metric



Summary

- To date, 4/6 subjects at the 9.0×10^{11} gc total dose have variable, localized MRI abnormalities at the site of vector administration
- There are no clinical correlates of these MRI abnormalities in the study outcome variables
- **Decision** – Lower the dose $\frac{1}{2}$ log to 2.85×10^{11} gc

Revised Trial Design, Lower Dose for Both Protocols

Treatment with AAVrh.10hCLN2

“NIH” protocol
n=16

“Parallel” protocol
n=8

1st dose cohort (Group A)
n=6 received original
“low dose”

7.5 x10¹⁰ gc/site
12 sites

Total dose **9.0 x10¹¹ gc**

Assess efficacy
parameters at 6, 12, 18
months

2nd dose cohort (Group B)
n=1 received ½ log lower dose
Remaining n=9 will receive ½
log lower dose

4.75 x10¹⁰ gc/site
12 sites

Total dose **2.85x10¹¹ gc**

Assess efficacy
parameters at 6, 12, 18
months

n=2 received original dose
(**9.0 x10¹¹ gc**)
n=1 received ½ log lower dose
(**2.85x10¹¹ gc**)

Remaining n=5 will receive
½ log lower dose

4.75 x10¹⁰ gc/site
12 sites

Total dose **2.85x10¹¹ gc**

Assess efficacy
parameters at 6, 12, 18
months