A Natural History Study of Mucopolysaccharidosis IIIA (MPSIIIA, Sanfilippo Syndrome Type A)

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MPSIIIA Disease Overview

- Autosomal recessive: mutations in *SGSH*, encoding heparan N sulfatase; over 70 mutations described
- Live birth incidence ~ 1 in 100,000
- Enzyme defect causes accumulation of heparan sulfate
- Clinical features are overwhelmingly neurological:
  - normal early infancy
  - developmental delays often first manifestations
  - severe behavioral disturbances are a prominent feature of middle childhood
  - progressive dementia leads to a “quiet phase” of withdrawal and developmental regression
  - survival to late teens / early 20s
- No ethnic predisposition
- Primary accumulation of the glycosaminoglycan (GAG) heparan sulfate triggers poorly understood pathological cascade with primarily CNS manifestations
- Pathomechanisms invoked include: secondary accumulation of toxic metabolites, neuroinflammation, disrupted growth factor signaling, dysregulated cell death

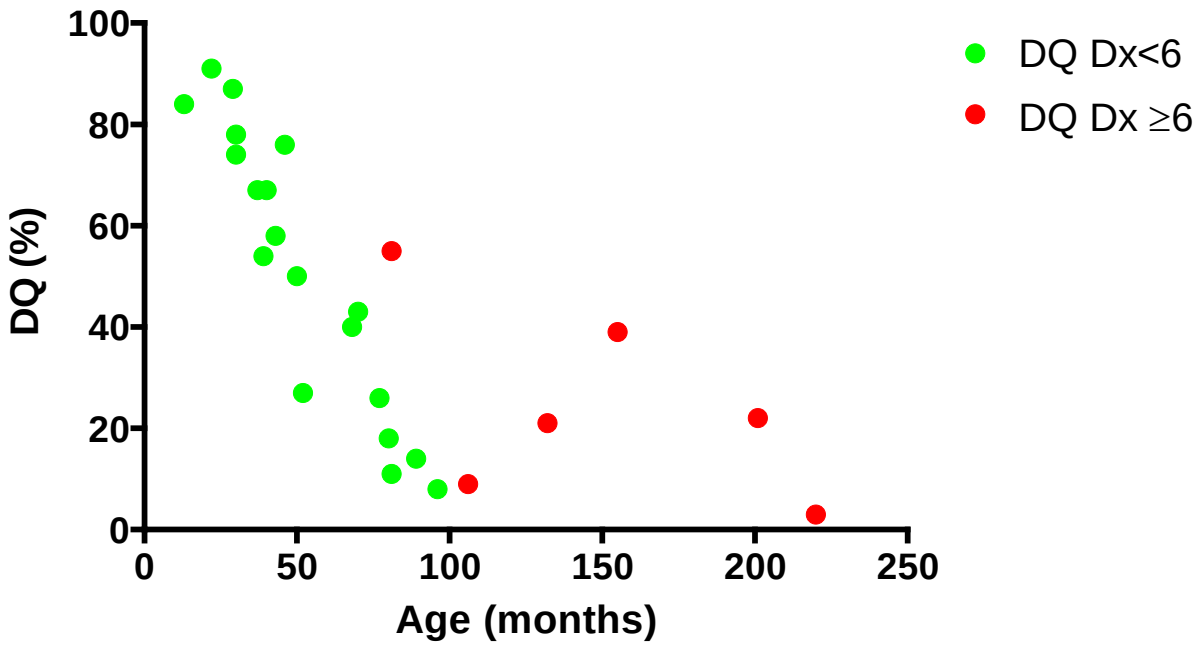
HGT-SAN-053 Natural History Study of MPSIIIA

- Description: An observational study with no investigational treatment
- Enrollment criteria
  - Confirmed MPSIIIA diagnosis
  - Calendar age ≥ 1 yr
  - Developmental age ≥ 1yr, estimated using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- Evaluations every 6 months for 12 months:
  - Comprehensive neurodevelopmental assessments
  - Brain imaging
  - Cerebrospinal fluid biomarkers
- Rationale:
  - To understand MPSIIIA disease spectrum
  - To measure disease progression over 12 months
  - To obtain insight into an appropriate patient population for trials of therapy
  - To identify candidate endpoints applicable in clinical trials
  - To generate a high quality set of data with potential utility as a historical control

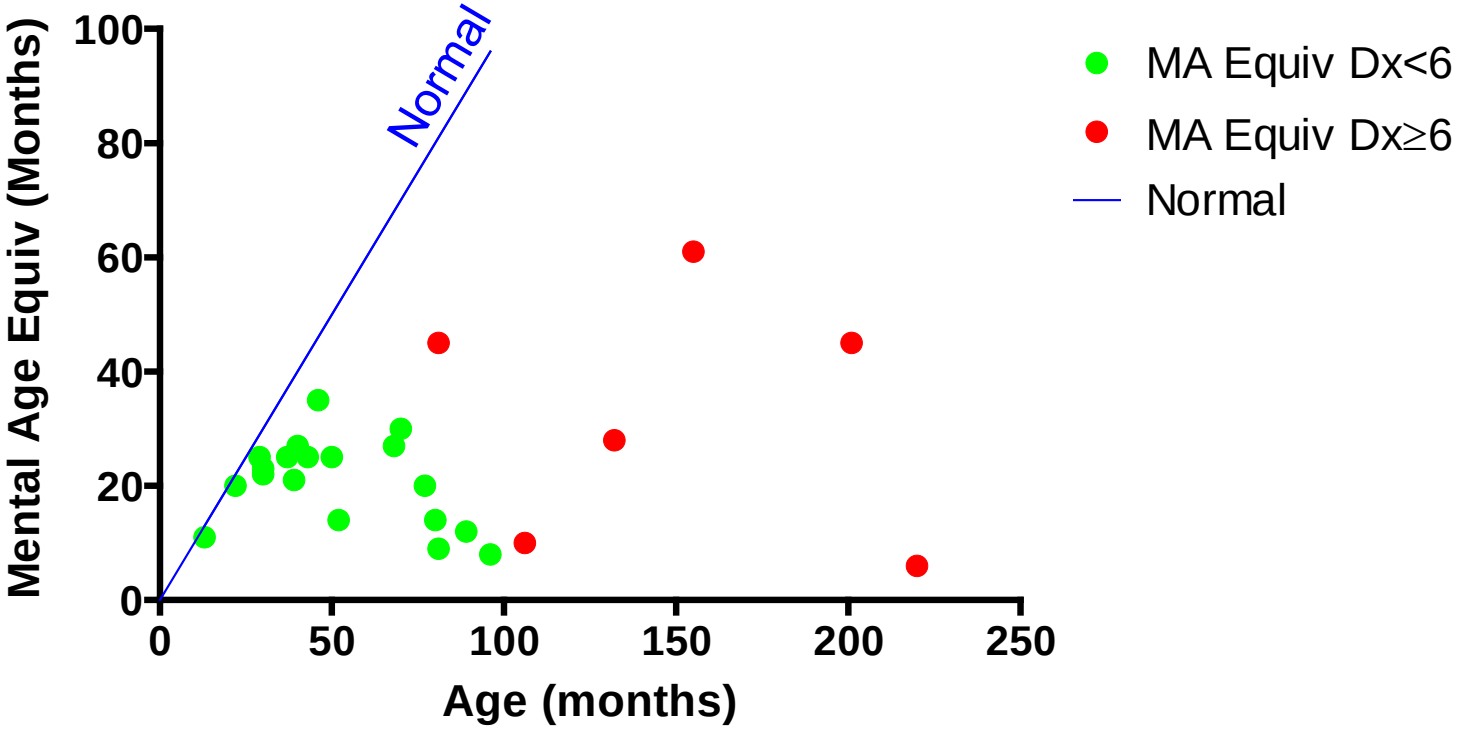
SAN-053 Developmental Assessment

- 25 children enrolled at a single site (U Minnesota)
- Neurodevelopmental assessment using either the Bayley Scales of Infant Development III (BSID), or Kaufman Assessment Battery for Children (KABC)
- For both the BSID and the KABC a total mental age equivalent (MA) was calculated for every participant in months
- To create a developmental quotient (DQ), total mental age equivalent (MA) was divided by chronological age in months (CA): DQ (%) = (MA/CA) x 100

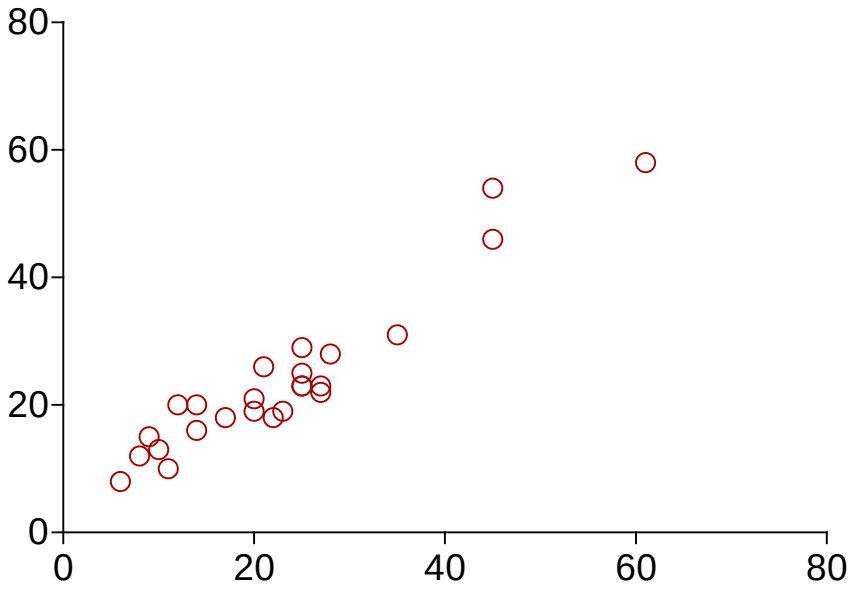
Baseline DQ plotted against age shows age-related decline
Patients diagnosed after age 6 may exhibit different rate of decline



Plot of mental age equivalence against calendar age reveals apparent plateau in mental age achieved @ 30 months in children diagnosed before age 6

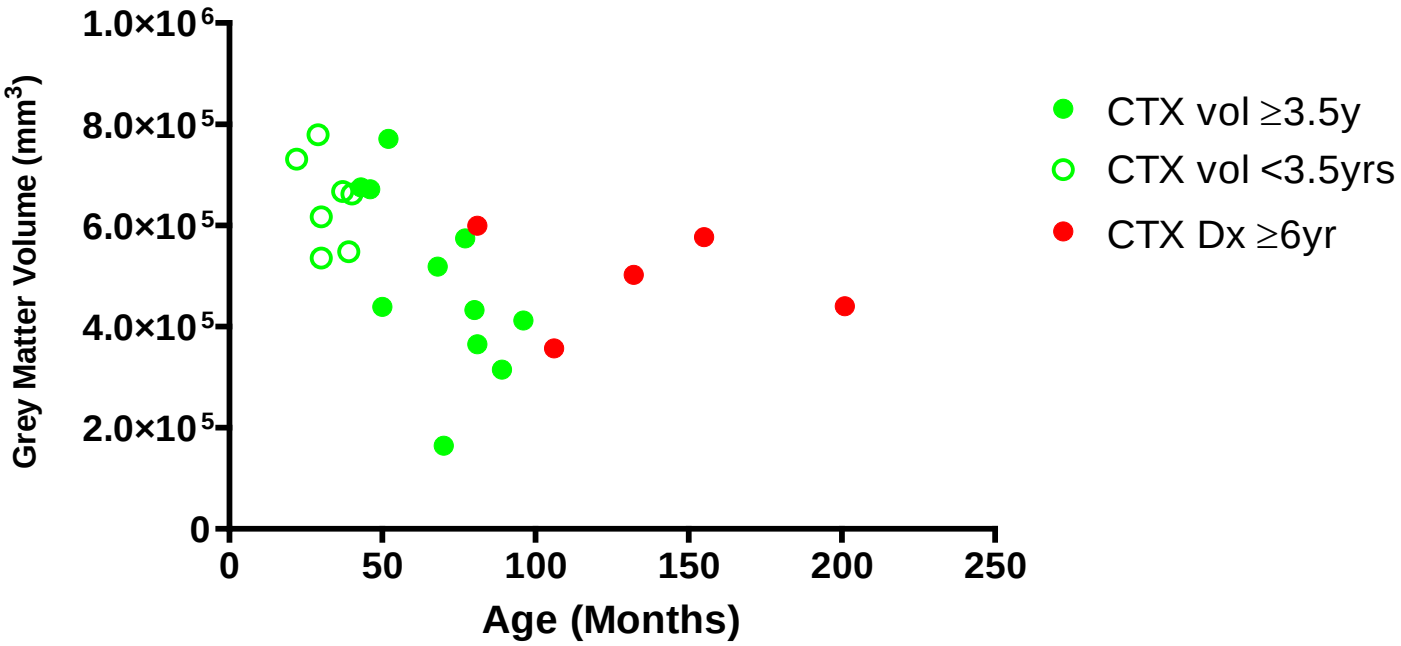


Developmental age equivalence independently assessed by VABS-II shows strong correlation with age equivalence calculated by BSID or KABC

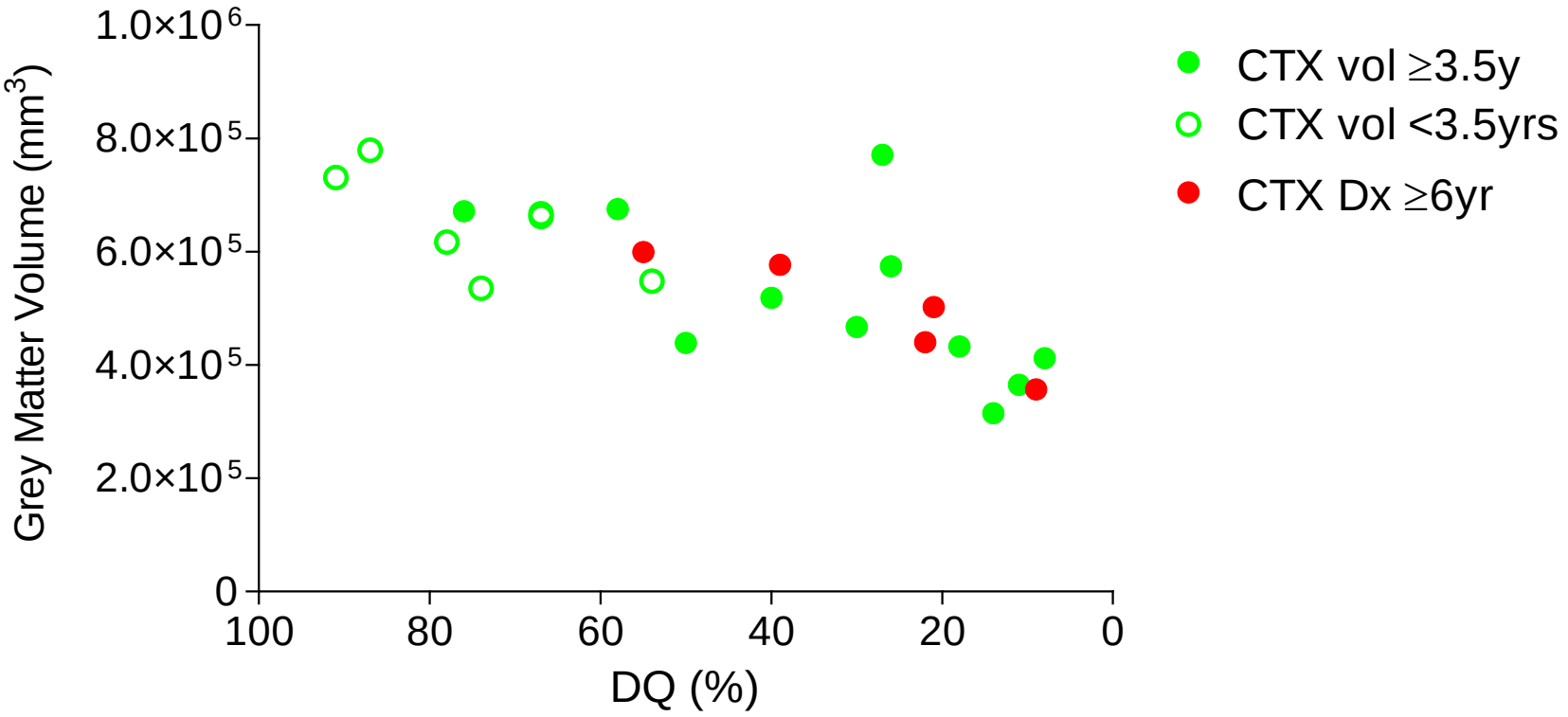


Automated brain magnetic resonance image (MRI) analysis using “Freesurfer” software

Data suggest decline in cerebral cortical volume with advancing age in children diagnosed before age 6



Cerebral cortical volume correlates with DQ



Summary of baseline clinical and imaging data

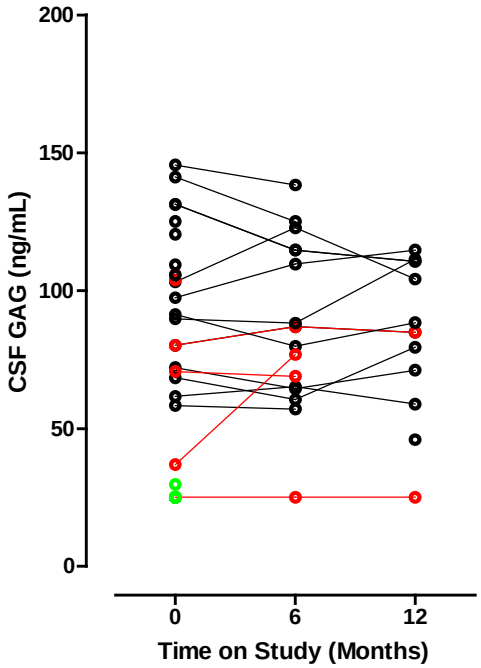
- Children diagnosed before and after the age of 6 years exhibit different patterns of disease progression, suggesting that later diagnosis is a surrogate for a phenotypic and prognostic difference
- In children diagnosed before the age of 6 years, cross-sectional data suggests a steady decline in DQ is evident from an early age
- This decline appears to reflect an arrest in the acquisition of new skills beyond the age of approximately 30 months
- Cortical grey matter volume exhibits age-dependent decline which correlates with loss of DQ

CSF Glycosaminoglycan (GAG) levels

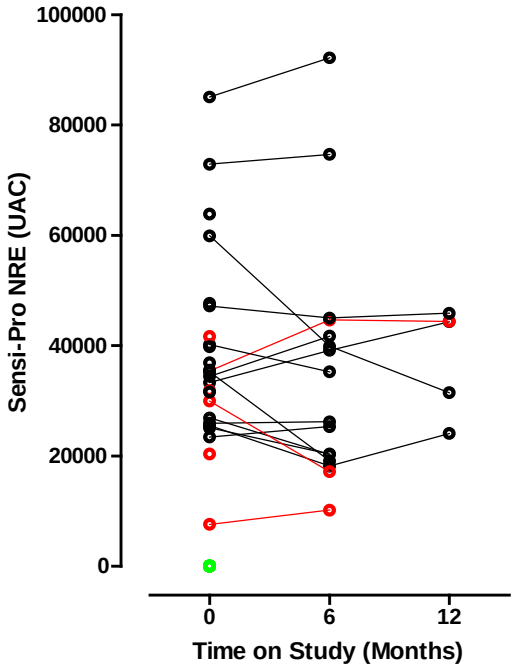
- Hypothesis: pathological heparan sulfate GAG accumulation in the brain is reflected in elevated GAG levels in the cerebrospinal fluid
- CSF GAGs were measured using 2 independent techniques:
  - Shire proprietary assay – measures a functional attribute of GAG
  - Zacharon assays – proprietary “Sensi-Pro” assay to measure MPSIIIA pathognomonic GAG via non-reducing end identification, as well as total heparan sulfate
- Samples collected from SAN-053 and healthy young adult controls were compared

CSF heparan sulfate levels measured using 3 different techniques reveal comparable patterns, and insight into trends over time

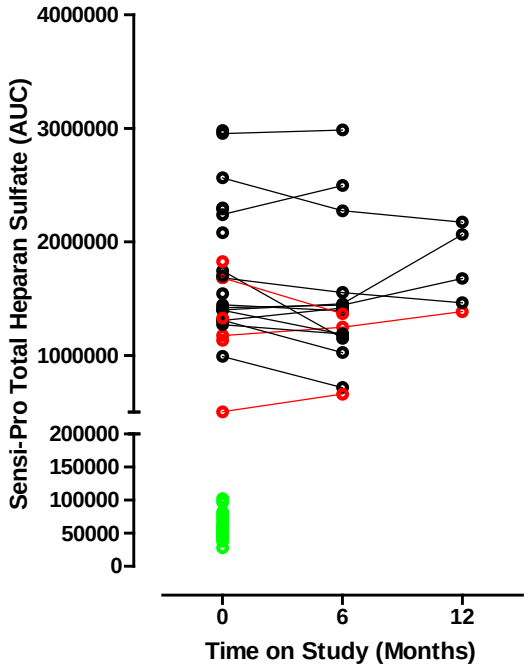
Shire
Heparan Sulfate



Zacharon Sensi-Pro
NRE

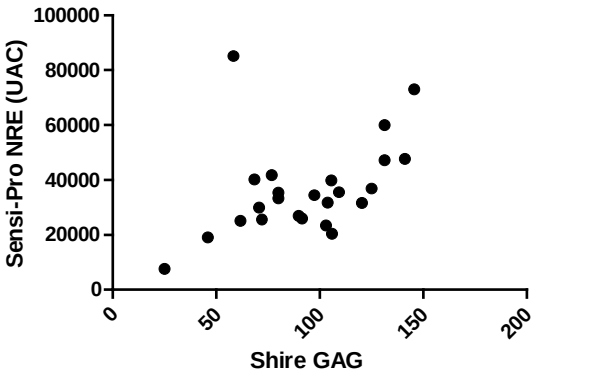


Zacharon Sensi-Pro
Total Heparan Sulfate

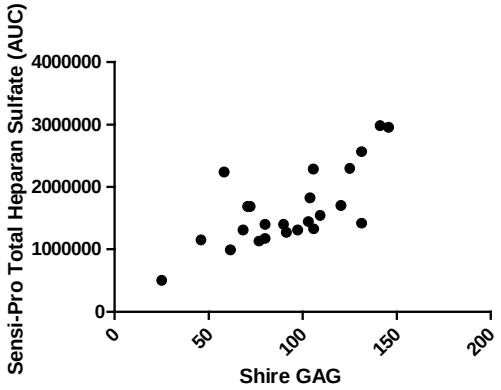


Dx < age 6 Dx ≥ age 6 Healthy Controls

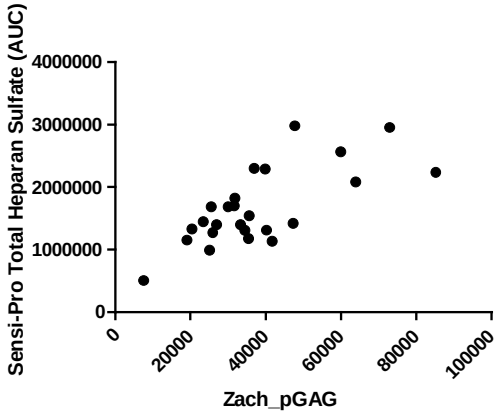
Correlation between 3 different heparan sulfate assays (baseline samples only)



Pearson r	0.4174
95% confidence interval	0.01679 to 0.7026
P value (two-tailed)	0.0424

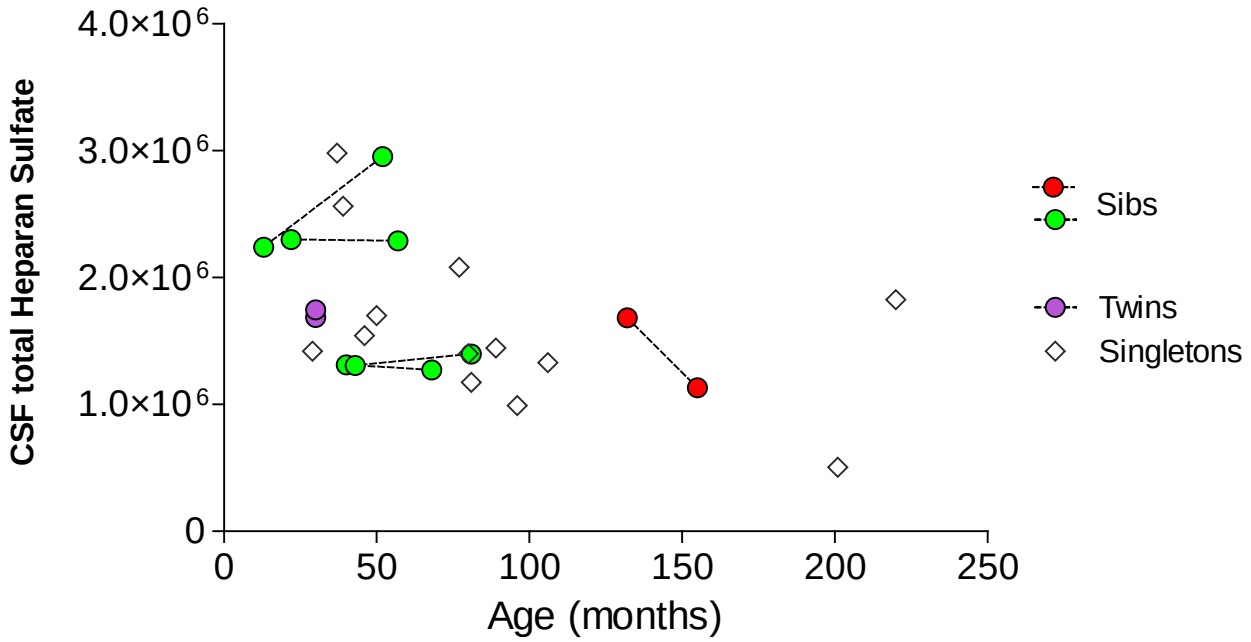


Pearson r	0.7090
95% confidence interval	0.4280 to 0.8650
P value (two-tailed)	0.0001



Pearson r	0.7175
95% confidence interval	0.4499 to 0.8669
P value (two-tailed)	P<0.0001

CSF Heparan Sulfate levels appear similar between sibling pairs



Identification of disease-associate biomarkers in MPSIIIA – a work in progress

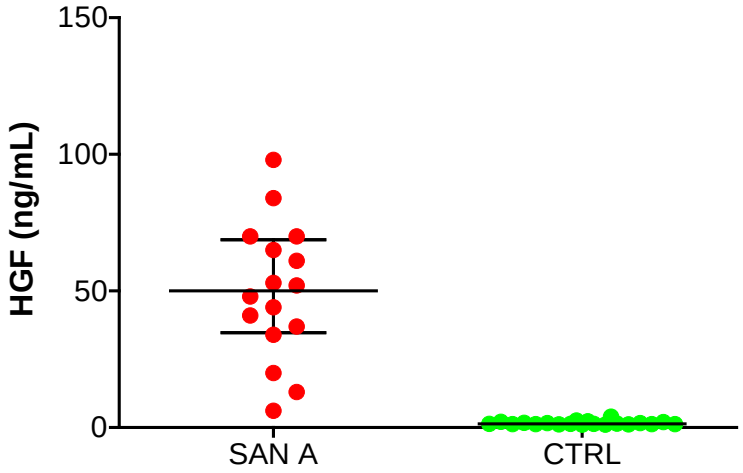
- "Selected Proteomics" by multiplexed immunoassays (luminex platform by Myriad / Rules-Based Medicine ~245 analytes)
  - RBM Discovery MAP 1.0 — 187-190 analytes
  - Selected markers from RBM OncoMAP — 45 analytes
  - RBM Custom Neuro/LSD Multiplex — 13 analytes

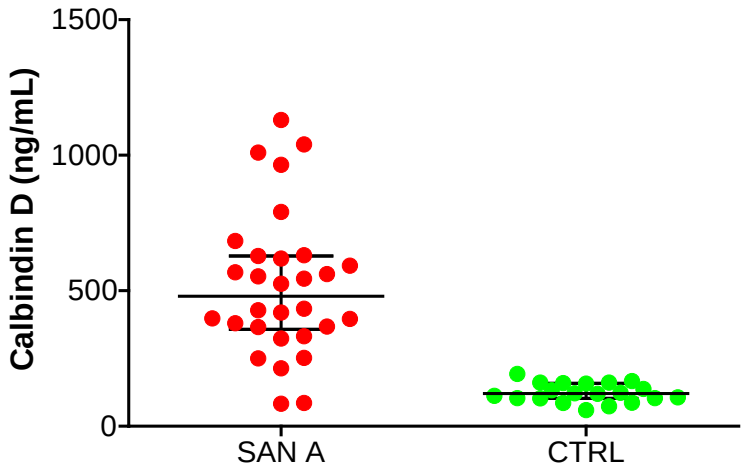
- Discriminant analysis performed, comparing data from MPSIIIA patients data with data from CSF collected prospectively from 20 young adult controls

Hepatocyte Growth Factor and Calbindin D

Hepatocyte Growth Factor
•Key role in regulation of dendritic spine morphology and synaptogenesis
•Receptor is c-Met – pathway implicated in mental retardation / ASD / macrocephaly complexes

Calbindin D
•Expressed in Purkinje cells & striatum
•Possible predictor of dementia in patients at risk for Alzheimer's Disease (Craig-Shapiro et al PLoS one 2011 6:e18850)

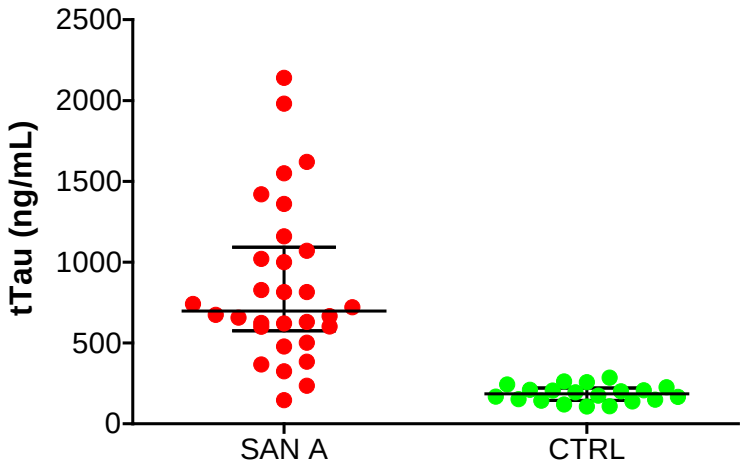


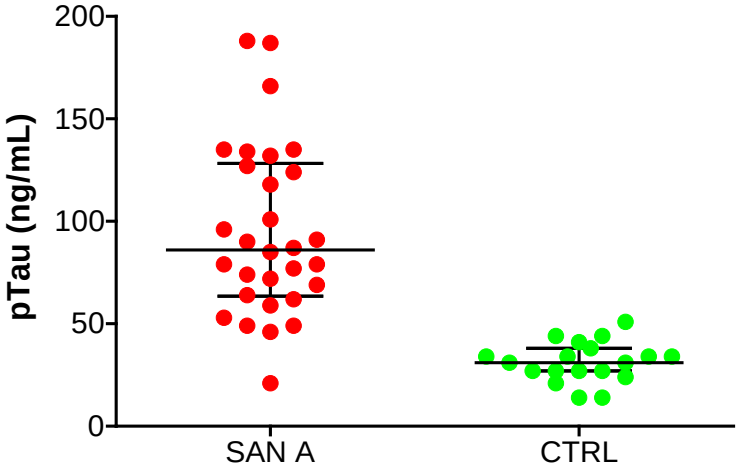


Total tau and phosphorylated tau

Total tau protein
•Elevated in several adult neurodegenerative diseases

Phosphorylated tau (p181)
•Age-dependent increase reported in brain of MPSIIIb mouse (Ohmi et al PNAS 2009 106:8332)





Conclusions and questions

- Baseline data from 25 MPSIIIA patients suggest arrest in cognitive development occurs in the majority of children, at around age 30 months
  - Does this correspond to a particularly vulnerable process in neurodevelopment – e.g., synaptogenesis?
  - What are the implications for the optimal timing of therapy?
- Cognitive decline correlates with brain cortical volume
  - Could cortical volume be an objective indicator of the pathological process with utility as a clinical trial endpoint?
- CSF heparan sulfate levels are elevated, and appear to remain at relatively constant levels for up to 12 months
- Preliminary screen identifies biologically plausible, disease-related candidate biomarkers

How do these preliminary results from the Natural History study help us to think about developing a therapy for MPSIIIA?

- Rationale:
  - To understand MPSIIIA disease spectrum
    - *Baseline data suggest 2 phenotypic patterns, with patients distinguished by age of diagnosis (genotype/phenotype studies will follow)*
  - To measure disease progression over 12 months
    - *Preliminary longitudinal data (not shown) suggest that interim conclusions inferred from the cross-sectional analysis are valid*
  - To obtain insight into an appropriate patient population for trials of therapy
    - *Attainment of a developmental plateau suggests that for maximal efficacy, treatment should be initiated as early during the plateau phase as possible*
  - To identify candidate endpoints applicable in clinical trials of experimental therapy
    - *Preliminary identification of biologically plausible CSF biomarkers and brain MRI patterns suggests that these may be useful adjuncts to clinical evaluation in assessing the impact of therapy*
  - To generate a high quality set of data with potential utility as a historical control

Acknowledgements

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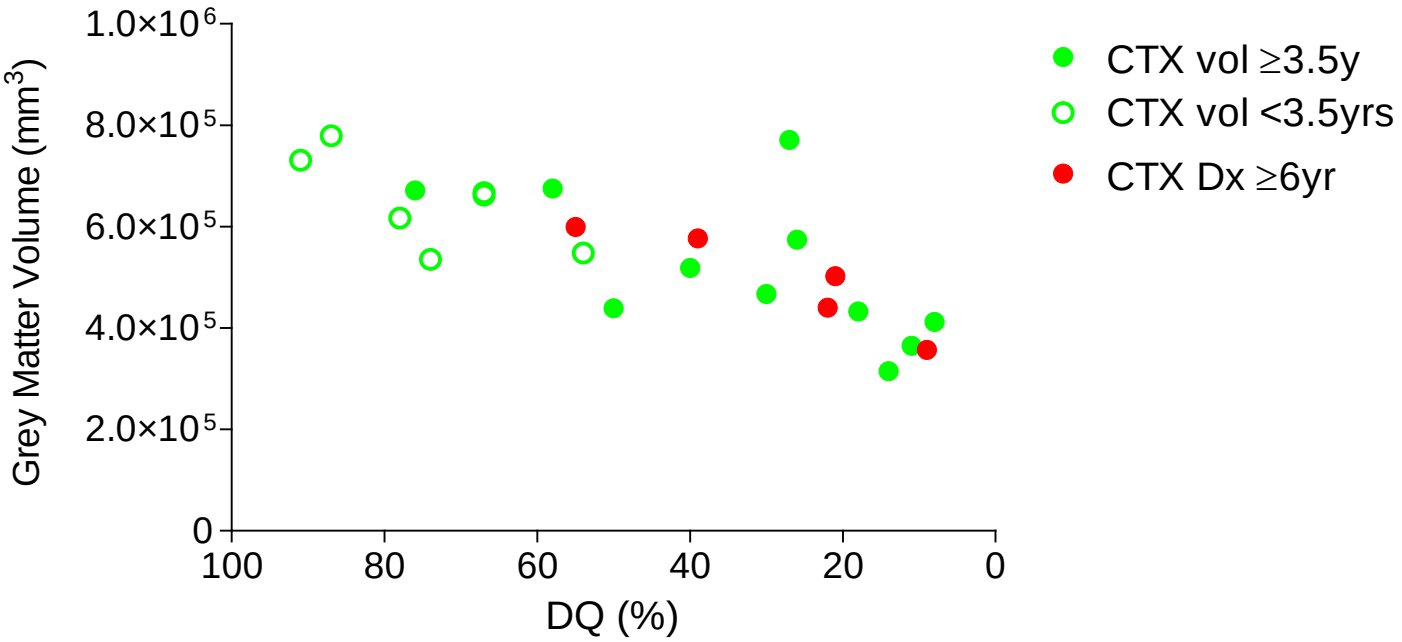
1.0×10^6
8.0×10^5
6.0×10^5
4.0×10^5
2.0×10^5
0
Grey Matter Volume (mm^3)
100
80
60
40
20
0
DQ (%)
CTX vol ≥3.5y
CTX vol <3.5yrs
CTX Dx ≥6yr