



## Disclaimer:

Presentation slides from the Rare Disease Workshop Series are posted by the EveryLife Foundation for Rare Diseases for educational purposes only. They are for use by drug development professionals and statisticians, and are not to be used to guide the prescribing or use of any of the drugs mentioned in the slides. To obtain information on a particular drug, refer to the drug labeling. Do not reproduce or distribute the slides (full set or any portion of) without the permission of the author.



**RARE DISEASE WORKSHOP SERIES**  
Improving the Clinical Development Process

# **X-linked Adrenoleukodystrophy: rationale and current assessment of markers to track progression**

November 8, 2011

Kathleen M. Zackowski, PhD

Assistant professor

Depts. of Physical Medicine and Rehabilitation, Neurology  
Kennedy Krieger Institute / Johns Hopkins University School  
of Medicine

# Adrenoleukodystrophy (ALD)

X-linked disorder - Xq28

incidence 1:17,000, all races affected

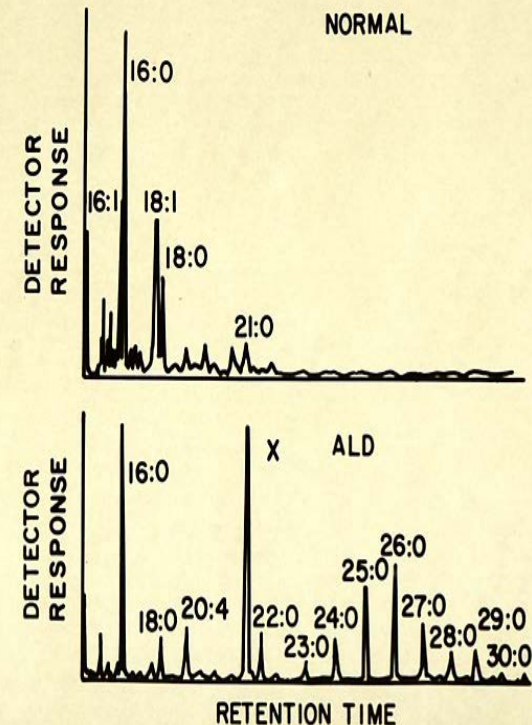
Peroxisomal ATPase Binding Cassette Protein (ABCD1)

Defect in peroxisomal beta oxidation

Accumulation of very long chain fatty acids (VLCFA)

Affects myelin, adrenal cortex, Leydig cells of the testes

FATTY ACID METHYL ESTERS OF BRAIN CHOLESTEROL ESTERS (GAS CHROMATOGRAPHY)



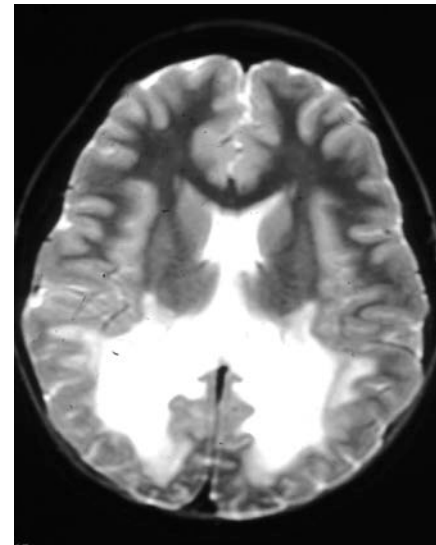
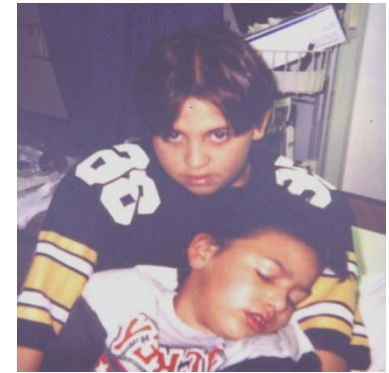
*Igarashi et al.*

*J Neurochem 26:851-860, 1976*

# Variable Manifestations (phenotypes) of ALD and Relative Frequency

- **Cerebral (35%)**
  - Diffuse inflammatory demyelination, rapid progression.
  - Childhood form (onset 4-8 years) most common
- **Adrenomyeloneuropathy (AMN) (40-65%)**
  - Distal axonopathy mainly in spinal cord.
  - Paraparesis in young adults, progress over decades
  - Cerebral disease occurs in 19-40%
- **Addison Disease only (20-30% at onset)**
  - Most develop AMN later
- **Asymptomatic**
- **>50% of heterozygous women develop AMN in adult years with increase incidence with age.**

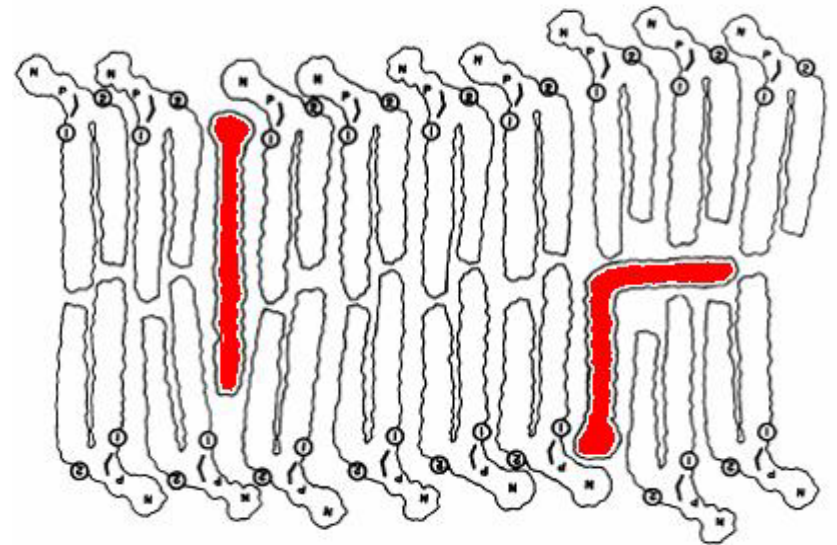
**Neither the gene defect nor the biochemical abnormality predicts the phenotype. A genetic modifier has been postulated**



# Role of VLCFA in pathogenesis

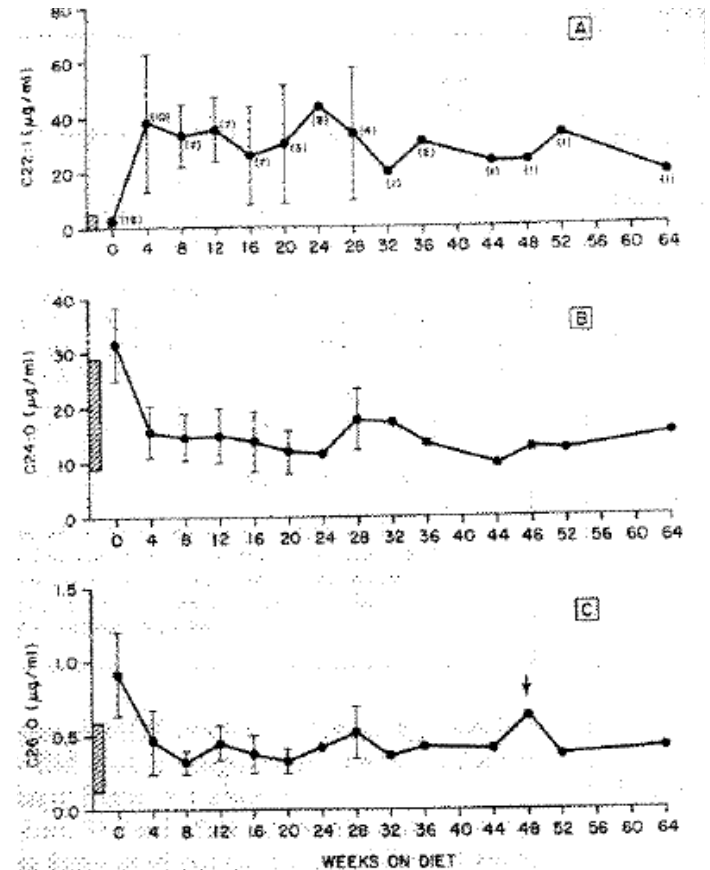
- Extremely insoluble in water and alters properties of membranes
- Viscosity of red cell membranes is increased
- Cultured adrenocortical cells—added VLCFA increased microviscosity of membranes and decreased cortisol release
- Inclusion in adrenocortical cells
- Binding with albumin is altered
- Inclusion of C26:0 in model membrane perturbs structure and stability
- Impairs stability of axonal or myelin membranes?
- Role as a trigger of immune response?

Schematic of C26:0 in PC Bilayers



# Lorenzo's Oil and low fat diet

- Dietary erucic acid therapy for X-linked adrenoleukodystrophy (Rizzo et al 1989)
  - 4:1 volume of oleic to erucic acid (Lorenzo's oil)
  - Plasma C26:0 decreased on GTE/GTO in 4-8 weeks
- 12 newly diagnosed cerebral individuals for 2-19 months.
  - Majority showed deterioration
- Issues
  - LO did lower VLCFA in plasma
  - Clinical response was less than encouraging
  - Could require months; myelin composition may not have changed



# Effect of Lorenzo's oil on manifestations of ALD

- No effect on childhood cerebral disease
- Adrenomyeloneuropathy – no definitive answer
  - Cappa et al (1990)– cerebral demyelination in only 2/11 treated individuals
  - Kaplan et al (1993)– VEP did not improve despite therapy
  - Aubourg et al (1993) (n=24); varying phenotypes including cerebral disease, boys, and heterozygotes; 9/14 men worsened
  - Van Geel et al (1999) (n=22); varying phenotypes including heterozygotes; generally progress
- All of these studies were uncontrolled
- Small number of individuals studied with a wide range of ages, disability, and phenotype
- Limited information on compliance and effective reduction of VLCFA
- In spite of these limits, the lack of clear improvement led to the presumption that oil was ineffective in all forms of ALD.
- **Preventative effect on presymptomatic boys**
  - *Moser et al. Arch Neurol. 2005 Jul;62(7):1073-80*

# Issues in studying AMN

**Disease burden at presentation**

**Slow disease progression**  
**Progression of disability**  
**occurs over decades**

**Limited markers**

**MRI**

**Clinical rating scales**

**Electrophysiologic studies**



	<b>Time from Diagnosis</b>	<b>Rankin Score</b>
Baseline	9.1±8.2	1.7±0.9
Last visit	16.2±8.9	2.9 ±1.1

*Van Geel et al Ann Neurol. 2001;49:186-94*

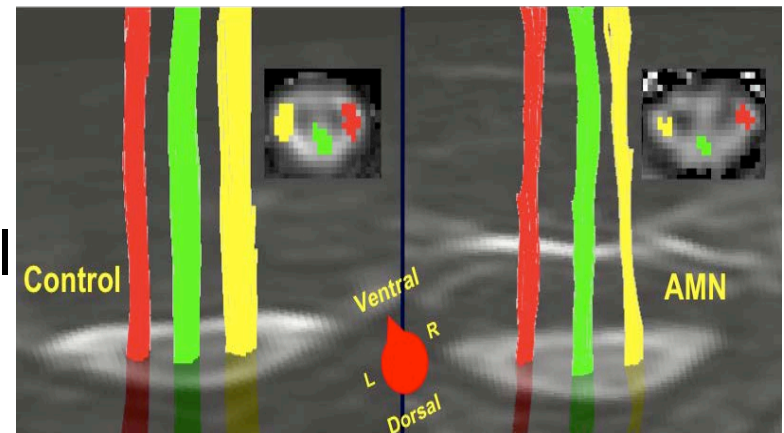
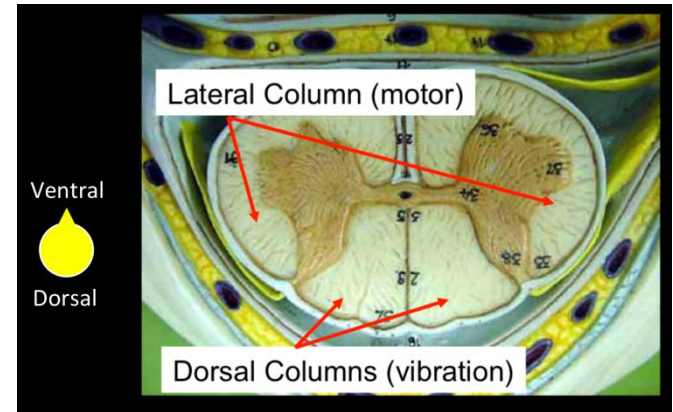


# Preventative therapy in AMN and Carriers

- **Placebo-controlled Study**
  - Diet and either GTO-GTE or a placebo
- **Planned enrollment 120 men with “pure” AMN and 120 symptomatic carriers**
- **4 year duration**
- **Yearly evaluation**
  - Neurologic exam
  - MRI of brain and cervical spinal cord
  - Nutrition
  - Quantitative Motion analysis
- **Outcome measures**
  - **Clinical status – Kurtzke FSS, EDSS, AADS**
    - Correlated with reduction in C26:0 levels
  - **Use of Quantitative functional measures and MRI**
- **Study related issues resulted in premature termination**

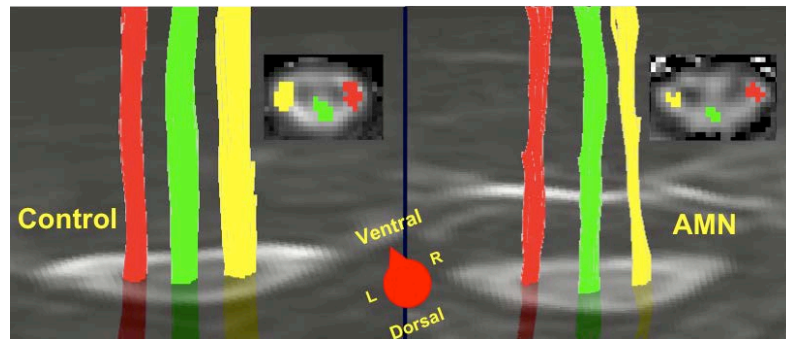
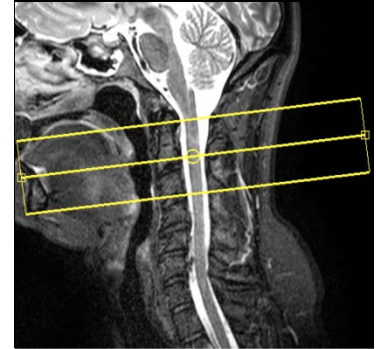
# Neuroimaging of the spine in AMN

- AMN
  - Affects spinal cord WM tracts
  - Slow, individualized progression
- Why use Diffusion Tensor Imaging?
  - DTI is sensitive to tissue microstructure
  - Use to assess relationship between spine and functional measures



# DTI Acquisition & Analysis

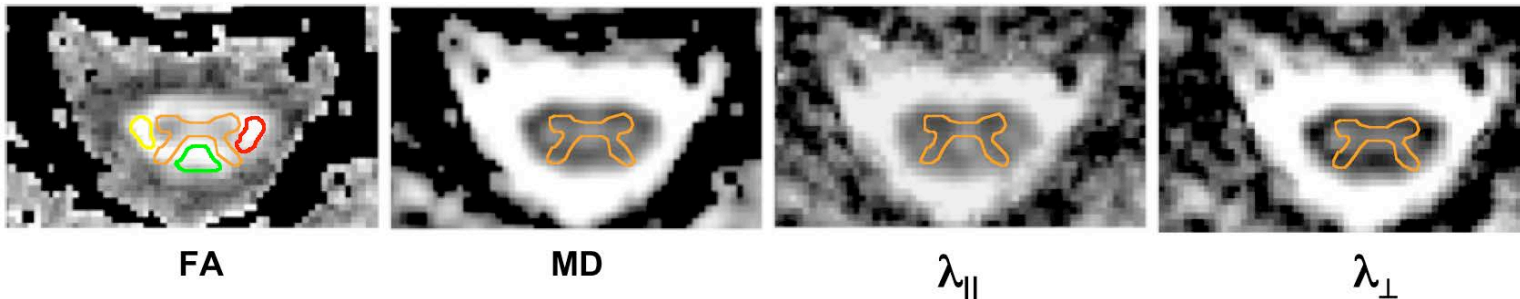
- Philips 3T MRI
  - Body coil excitation, 16-channel neurovascular coil for reception
- DTI
  - Multi-slice spin echo with single-shot EPI
  - 5 avg. minimally weighted and 16 diffusion-weighted volumes ( $b = 500 \text{ s/mm}^2$ )
  - TR/TE = 3000/58 ms
  - Sense factor 2
  - Nominal resolution: 1.5 mm x 1.5 mm x 3 mm, 16 slices, 2 averages
  - Scan time: 1 min per average



## DTIStudio – fiber tracking

ROIs seed fiber tracts

- Connects similar voxels
- Angle < 60 deg.
- FA value > 0.2



# Clinical Evaluation

	Number	Age	Age Range
Men	20	41.1 yrs	22 – 58 yrs
Women	20	52.1 yrs	39 – 68 yrs

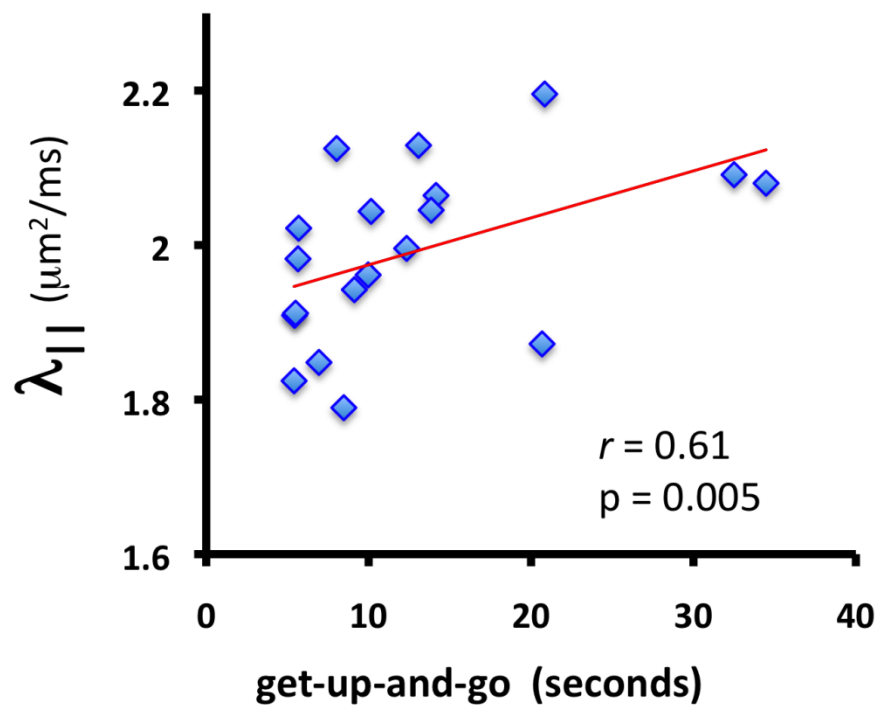
## Clinically evaluated

- Kurtzke Expanded Disability Scale (EDSS)
  - Focused only on scores 1 – 6.5
- Functional measures
  - Timed get up and go
  - Walking speed
  - Vibration sensation
  - Balance (eyes open feet apart)
  - Sit-to-stand
  - Hip flexion strength

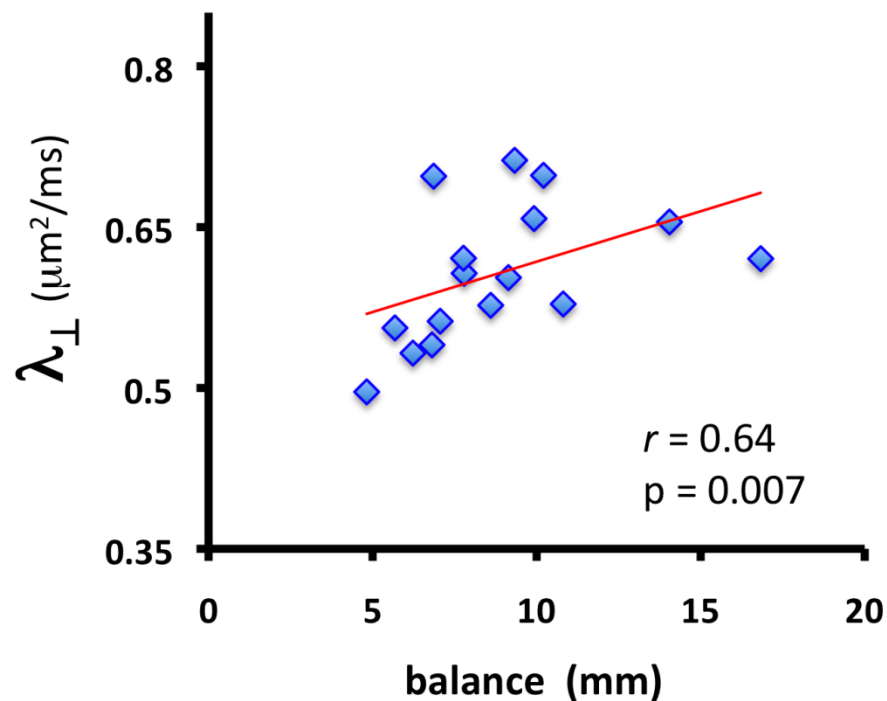
# Clinical Correlations: Men

## Dorsal Column

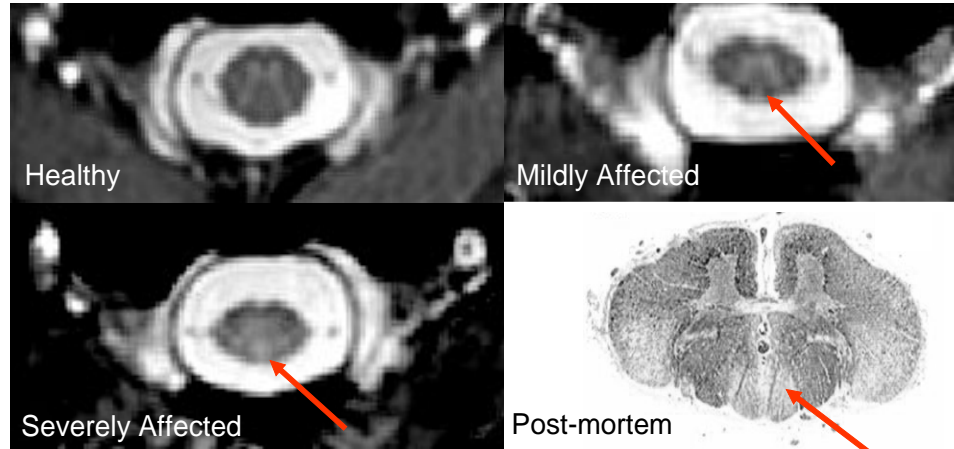
a)



b)

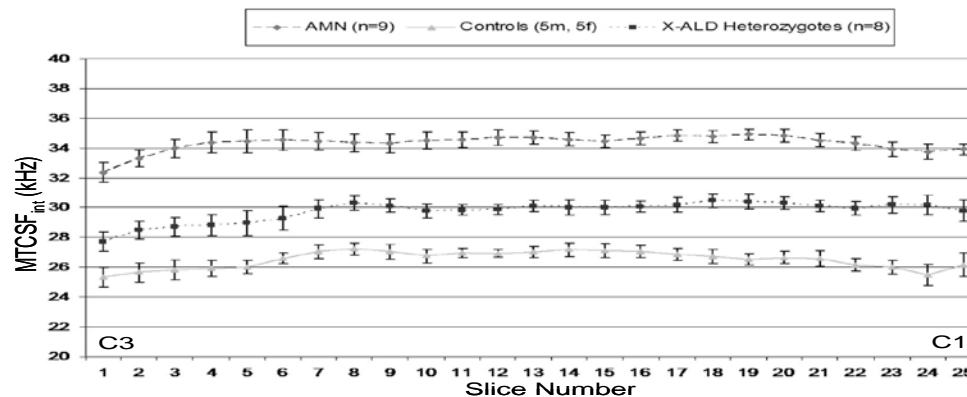


# Magnetization Transfer Imaging in AMN Trials



MT weighted Images

Post-mortem Reprinted with permission of Powers J, et al.

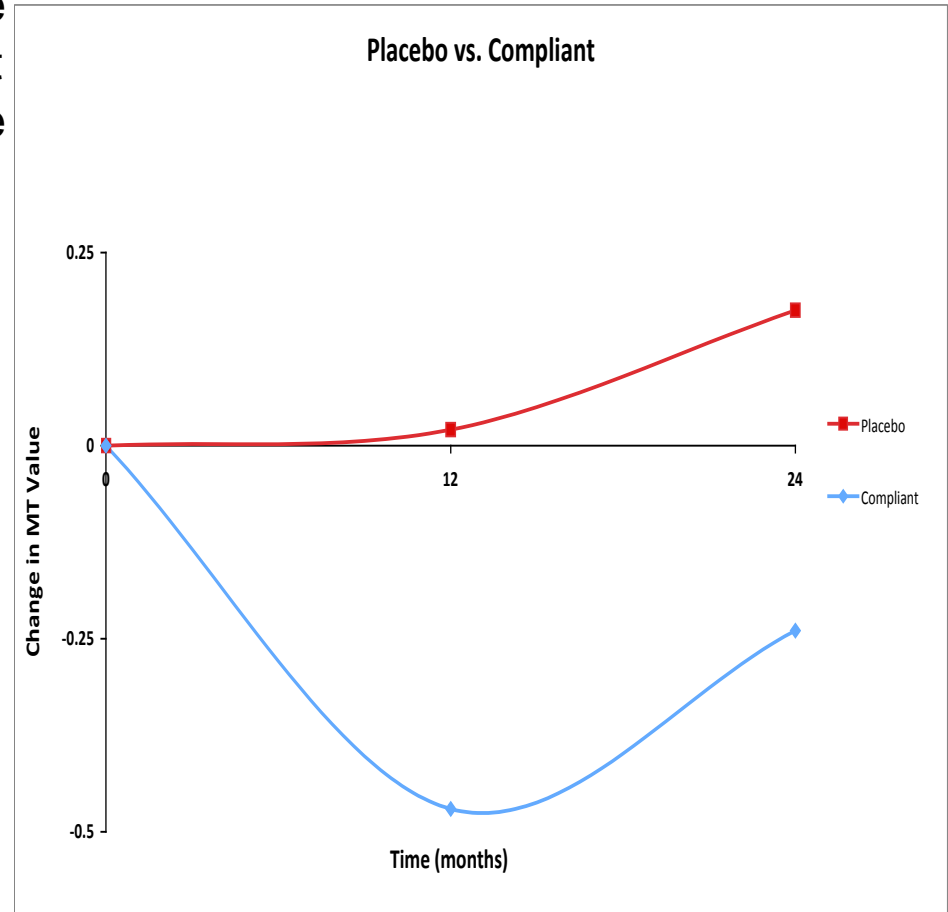


Diagnosis (mean ± SD)	AMN (34.34 ± 1.03)	Heterozygotes (29.76 ± 1.03)
Heterozygotes (29.76 ± 1.03)	p < 0.001	
Controls (26.82 ± 1.38)	p < 0.001	p < 0.001

# Magnetization Transfer Imaging

## Lorenzo oil Placebo trial

- MT MRI data were obtained in the dorsal column for each participant at baseline, 12 and 24 month time points.
- Defined  $\Delta$ MT as the difference in mean MT value between baseline/12 months and baseline/24 months
- Positive  $\Delta$ MT indicates greater abnormality at the 2<sup>nd</sup> time point [reflective of worsening]
- Negative  $\Delta$ MT indicates less abnormality at the 2<sup>nd</sup> time point [reflective of normalization]



# Conclusions on emerging imaging technologies in AMN and Lorenzo oil

- Strong correlation between tract-specific DTI-derived metrics and clinical dysfunction.
  - Stronger correlations in men than women
  - Magnetization Transfer Weighted Imaging demonstrated correlation with severity and longitudinally correlated with reduction in plasma very long chain fatty acids
- Ability to probe the structure-function relationship in patients with AMN may improve understanding of the pathologic abnormalities.
- Has promise for use in evaluating Lorenzo's oil and other therapeutic interventions
  - May allow for shorter trials
  - Objective marker of disease
  - Ability to determine degree of disease burden

# Acknowledgements

- Patients and their families

- Ann Moser
- Kathy Zackowski
- Jennifer Keller
- Seth Smith
- Aliya Gifford
- Richard Jones
- Lena Bezman
- Kim Hollandsworth
- Annette Snitcher
- Dinishia Pickford
- Katy Gibbons
- Steven Steinberg
- Sakkubai Naidu
- Rebecca Vaurio
- Tara Palmiero

N. Hong Brereton  
Ali Fatemi  
Florian Eichler  
Prachi Dubey  
Asif Mahmood

Westat  
Ros Hennessey  
Robert Harris

Funding provided by  
NIH, GCRC, Myelin  
Project, ELA, ULF

