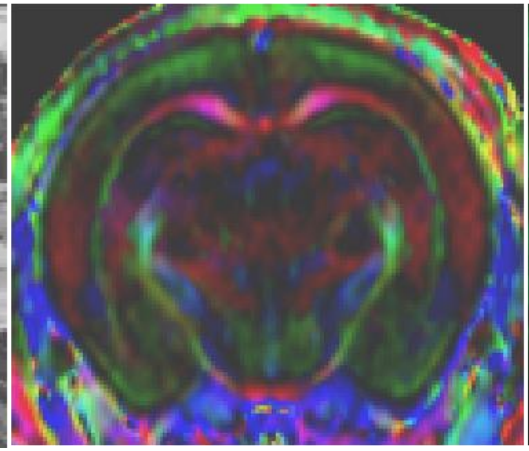
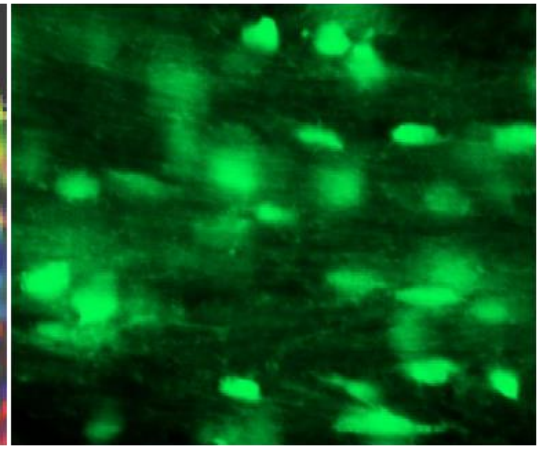
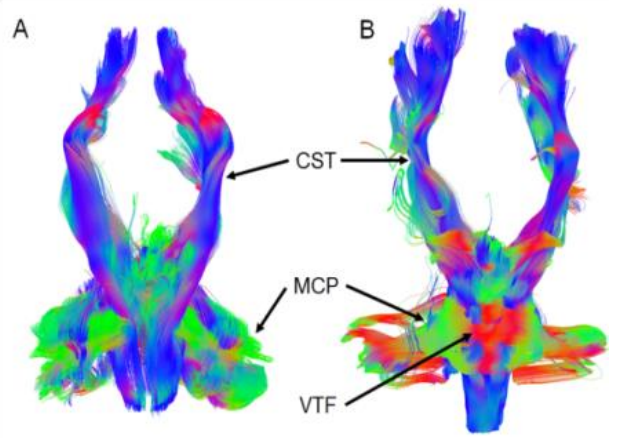






Moser Center for Leukodystrophies

at Kennedy Krieger Institute

A Certified Leukodystrophy Care Network (LCN) Center of Excellence

Hugo Wolfgang Moser 1924-2007

- *Son of a Viennese actress and Jewish German art collector*
- *Spent most of childhood as a refugee fleeing Nazis till arrival to US in 1940*
- *Served in WWII and Korean war*
- *Got Recommendation Letter from Albert Einstein to enter medical school*
- *Trained at Mass General Hospital (Harvard)*
- *President of KKI between 1976-88*
- *Through studying neurochemistry essentially established the field of leukodystophies*
- *Survivor guilt was perhaps his thrive to help those with orphan diseases.*

Moser Center for Leukodystrophies
at Kennedy Krieger Institute

Rehabilitation Medicine

Neurodiagnostics and treatment

Physical, Occupational Therapy

Social Counseling

Bladder Management

Behavioral Psychology

Endocrine evaluation and treatment

Genetic Counseling Family planning

Clinical Laboratory testing

Clinical Team

LBSL Clinical Research Study:

Amena Smith, MD, PHD

Miriam Kaufman

Connor Murray

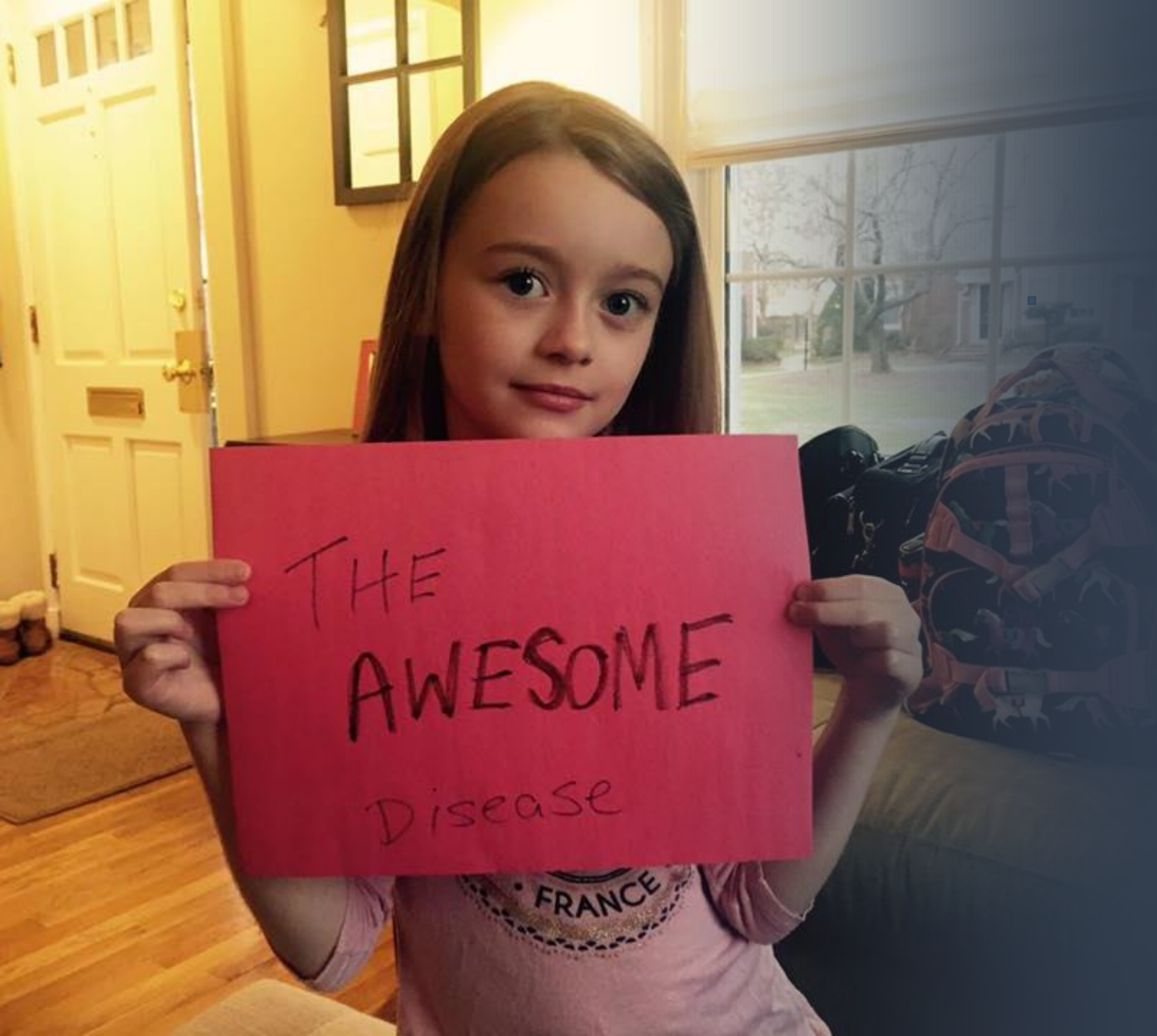
Chris Joseph, DPT

Jennifer Keller, DPT

Amy Bastian, PhD, CSO

Laboratory Research Team

- Christina Nemeth Mertz, PHD
- Sophia Tomlinson
- Melissa Rose
- Oscar Larrazo
- Carol Tiffany, MSc
- Benjamin Theisen, MD student
- Bela Turk, MD
- Philippe Hubo, MD student
- Paul Watkins, PhD
- Richard Jones, PhD
- Ann Moser



Leukoencephalopthy with Brainstem and Spinal Cord Involvement and Lactate Elevation

Ali Fatemi

Moser Center for Leukodystrophies
at Kennedy Krieger Institute

A New Leukoencephalopathy with Brainstem and Spinal Cord Involvement and High Lactate

Marjo S. van der Knaap, MD, PhD,[1]
Patrick van der Voorn, MD,[1,2]
Frederik Barkhof, MD, PhD,[3]
Rudy Van Coster, MD, PhD,[4]
Ingeborg Krägeloh-Mann, MD,[5]
Annette Feigenbaum, MD,[6] Susan Blaser, MD,[7]
Johan S. H. Vles, MD, PhD,[8] Peter Rieckmann, MD,[9]
and Petra J. W. Pouwels, PhD[10]

We identified eight patients with a distinct magnetic resonance imaging pattern of inhomogeneous cerebral white matter abnormalities and selective involvement of brainstem and spinal tracts. Proton magnetic resonance imaging showed increased lactate in the abnormal white matter. Clinically, the patients had slowly progressive pyramidal, cerebellar, and dorsal column dysfunction. The uniform, highly characteristic magnetic resonance imaging pattern and the similarities in clinical and magnetic resonance spectroscopy findings provide evidence for a new disease entity. Autosomal recessive inheritance is likely.

Ann Neurol 2003;53:252–258

Prof. Marjo van der Knaap

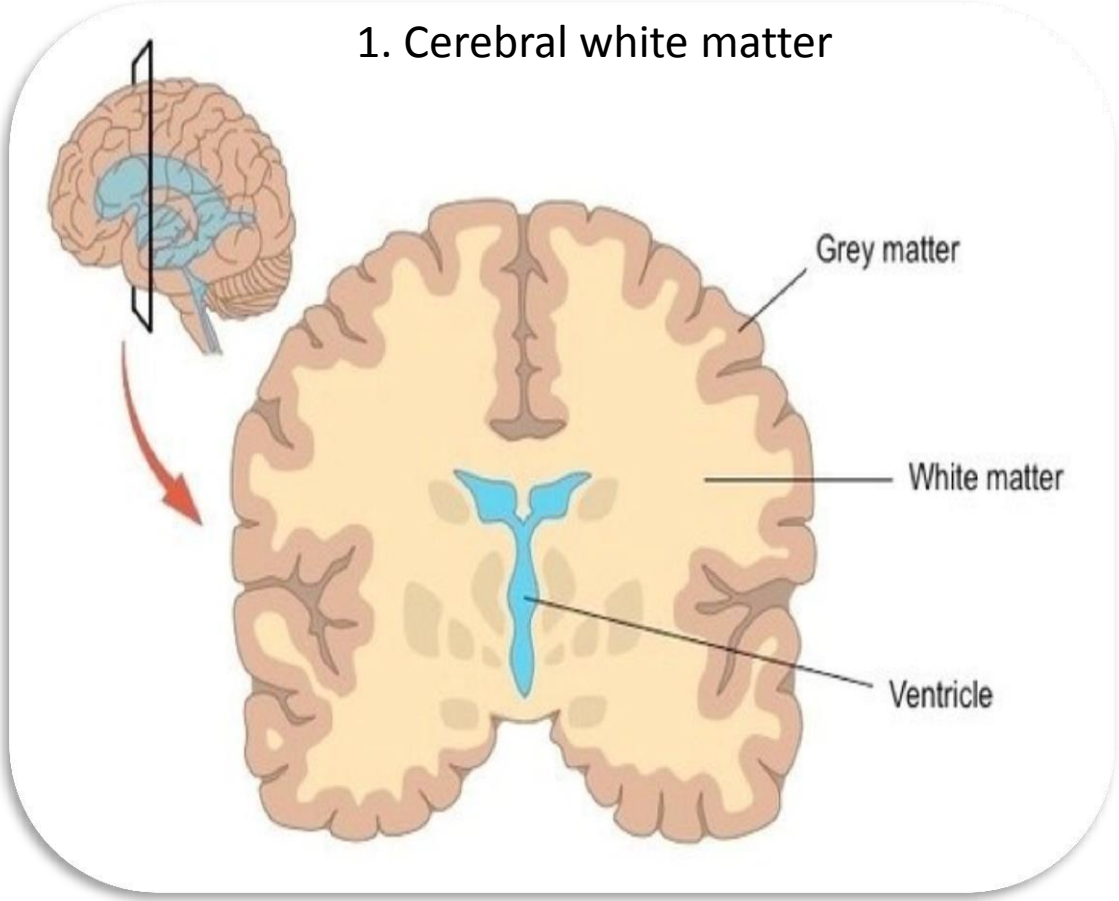
nature genetics

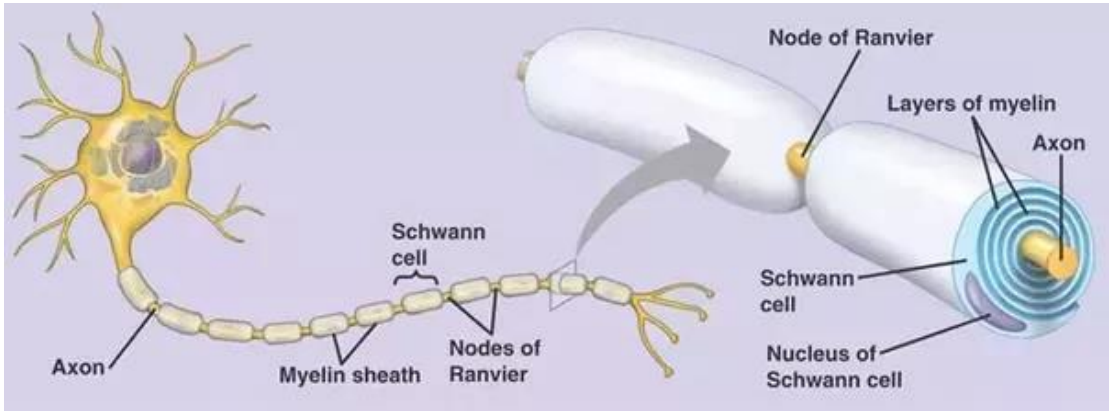
Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation

Gert C Scheper[1], Thom van der Klok[1], Rob J van Andel[1], Carola G M van Berkel[1], Marie Sissler[2], Joél Smet[3], Tatjana I Muravina[4], Sergey V Serkov[5], Graziella Uziel[6], Marianna Bugiani[6], Raphael Schiffmann[7], Ingeborg Krägeloh-Mann[8], Jan A M Smeitink[9], Catherine Florentz[2], Rudy Van Coster[3], Jan C Pronk[10] & Marjo S van der Knaap[1]

The Anatomy and MRI Signature of LBSL

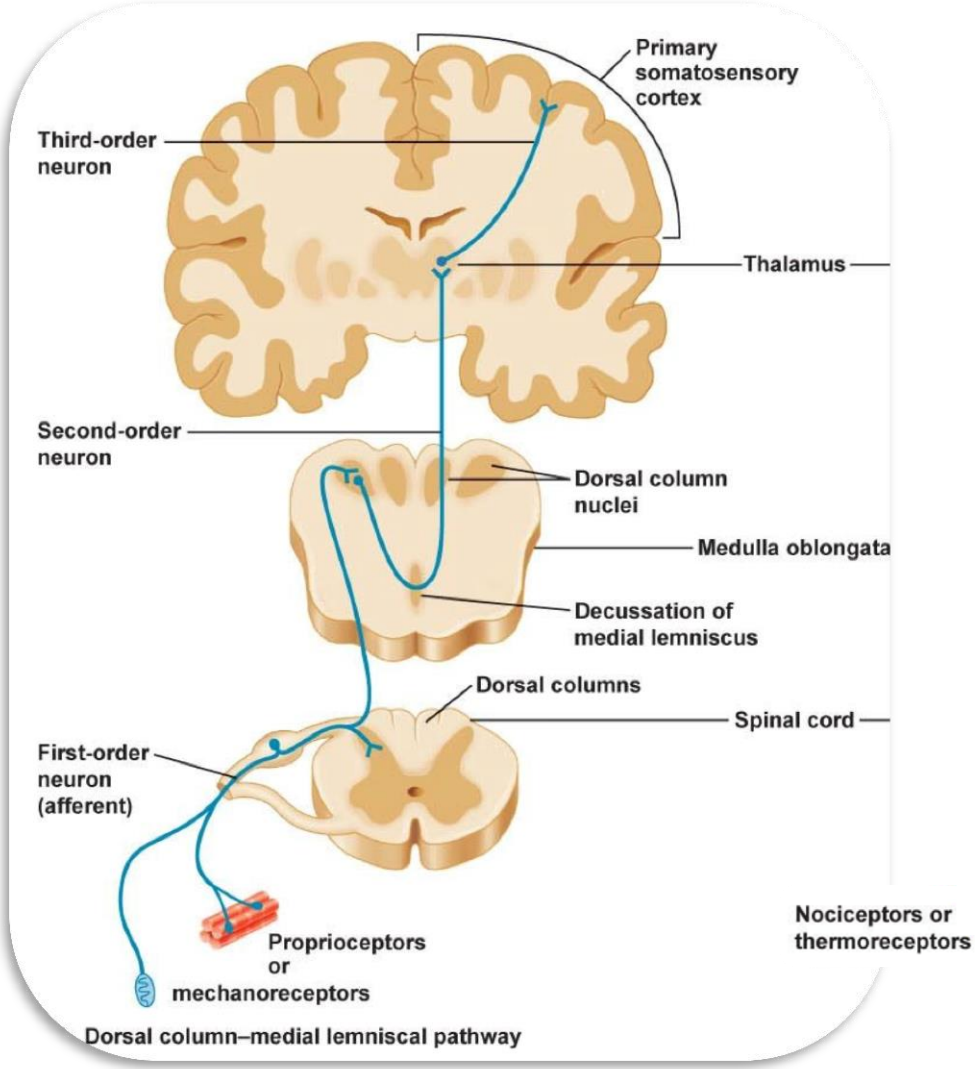
1. Cerebral white matter



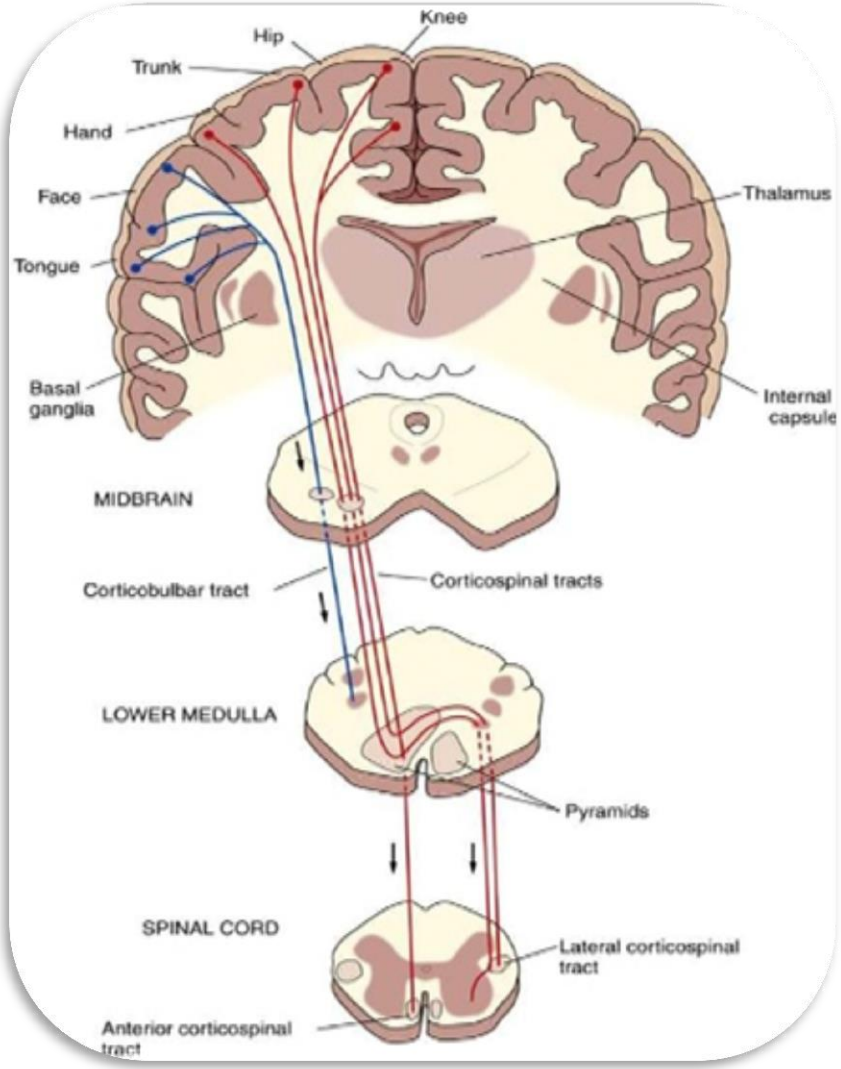


The Anatomy and MRI Signature of LBSL

2. vibration/positional sense tract

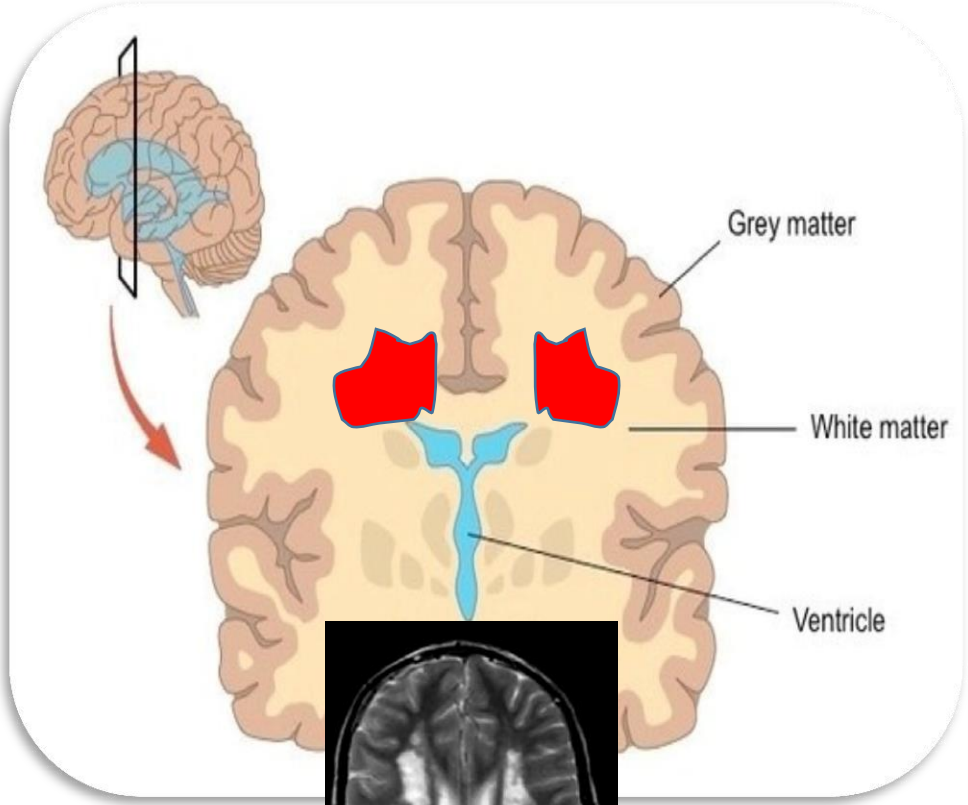


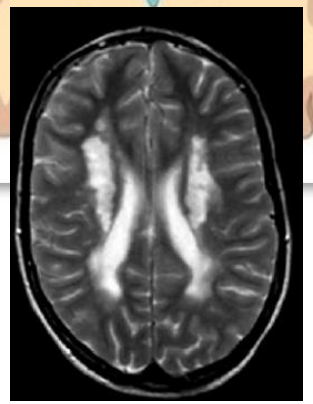
3. Motor tract



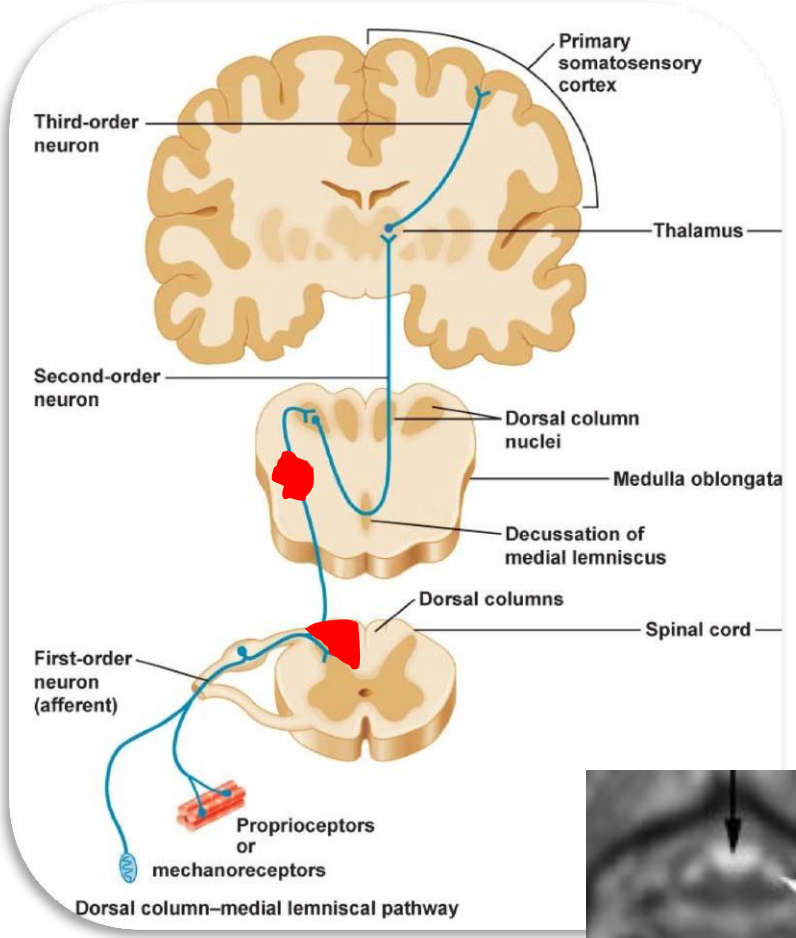
The Anatomy and MRI Signature of LBSL

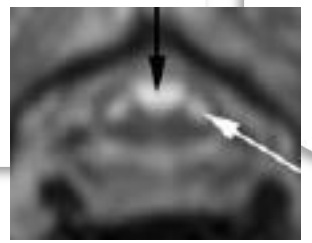
1. Cerebral white matter



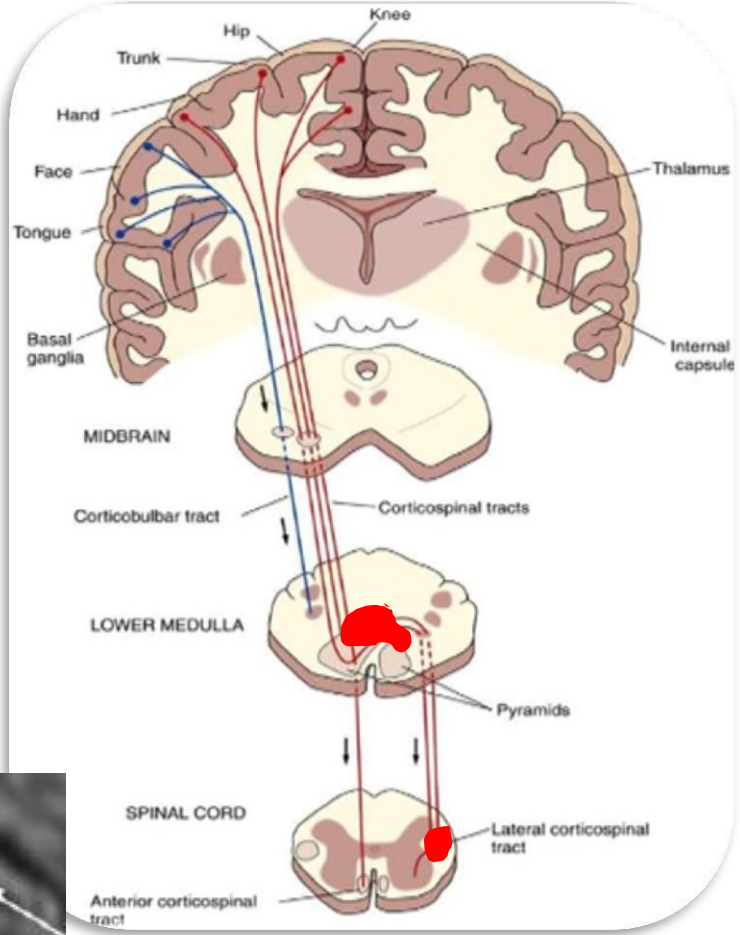


2. vibration/positional sense tract





3. Motor tract



Forms of LBSL

Neonatal 

Infantile 

Childhood 

Adolescent 

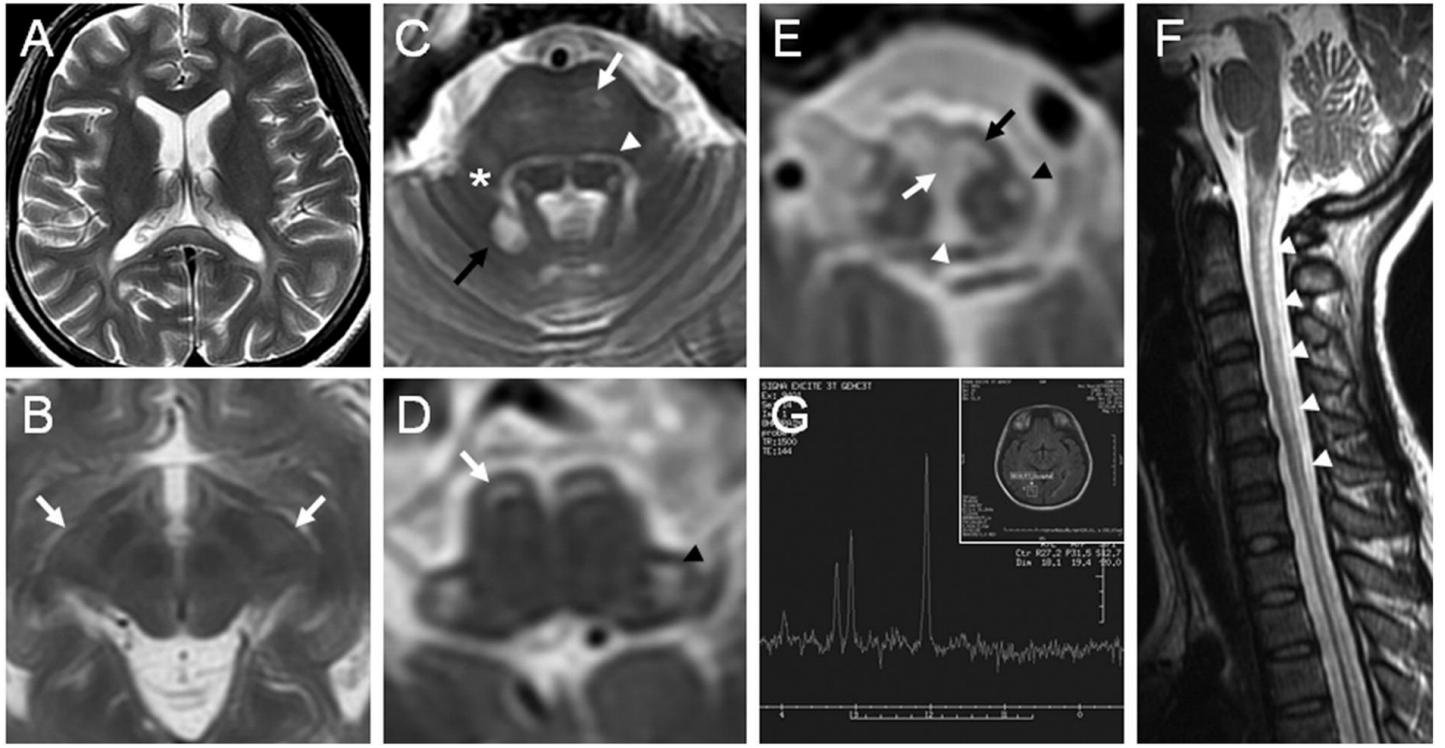
Adult 

Childhood Onset Form

- Normal initial development
- Often episodic decline in balance – falling often, getting wobbly, slower in speed
- Slowly progressive stiffness of the legs = spasticity
- Some individuals have clumsiness and hand tremors
- Gross cognitive function appears normal during childhood. Very limited knowledge about long-term outcome show difficulty in memory and processing speed.

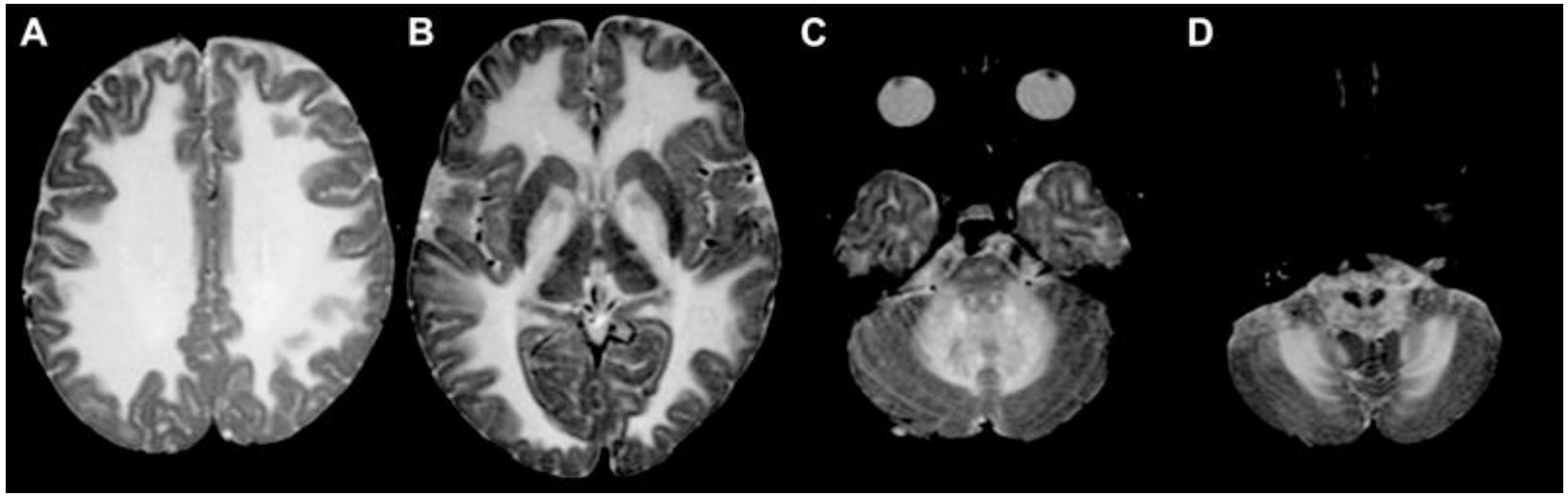
Adolescent/Adult Onset Forms

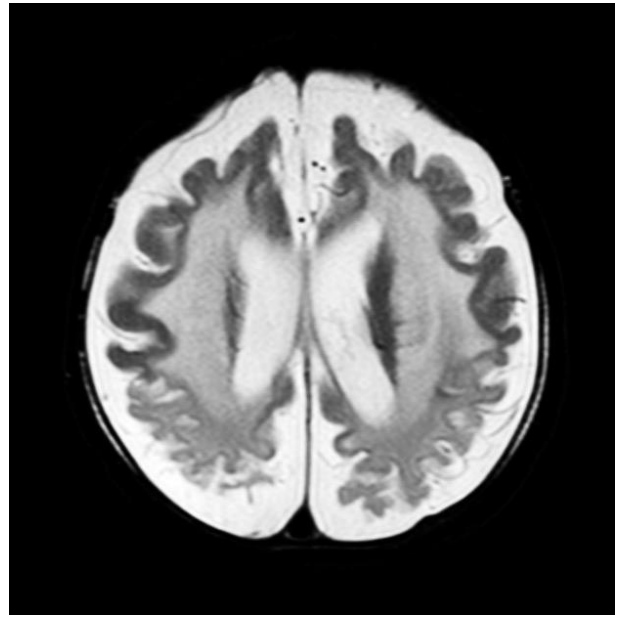
- Normal development
- First symptoms in teen years
- All reported cases were first balance issues
- Slowly progressive stiffness in legs = spasticity
- At least one individual known with cognitive decline in her 30s.
- Peripheral neuropathy



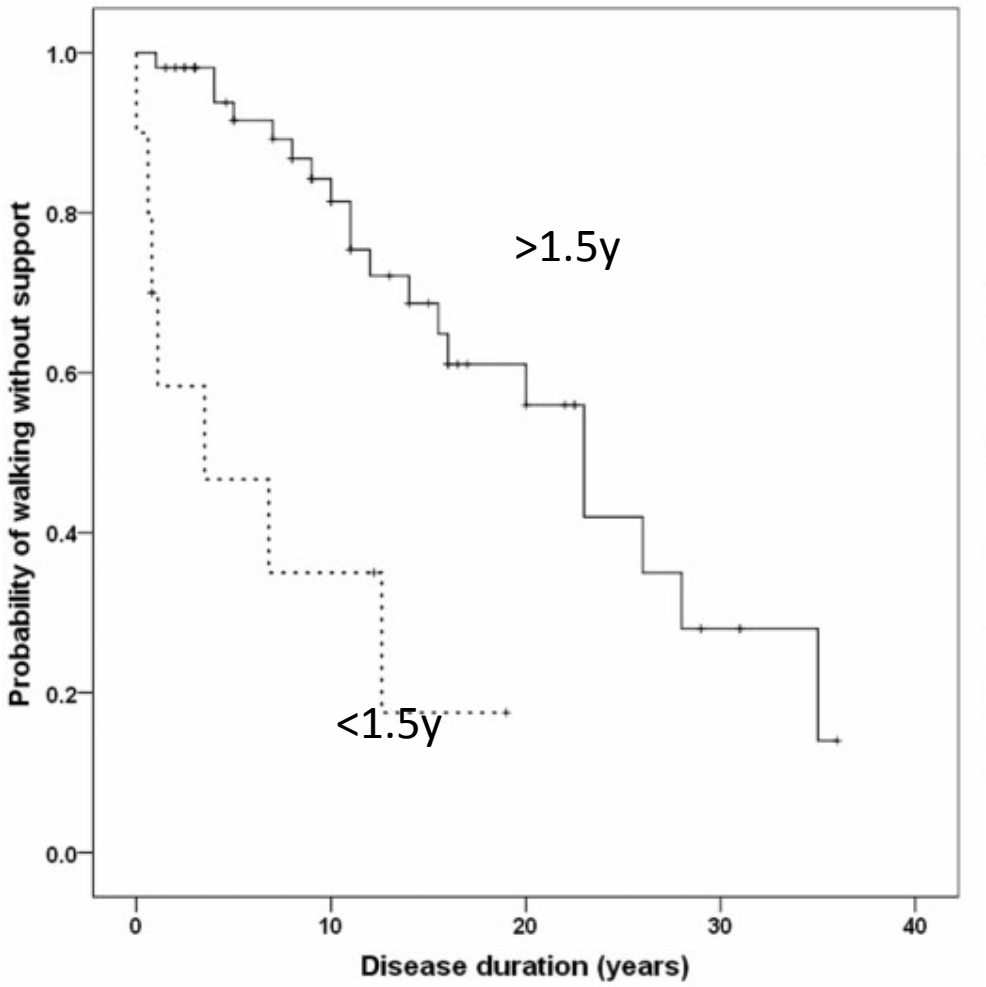
Neonatal early infantile form

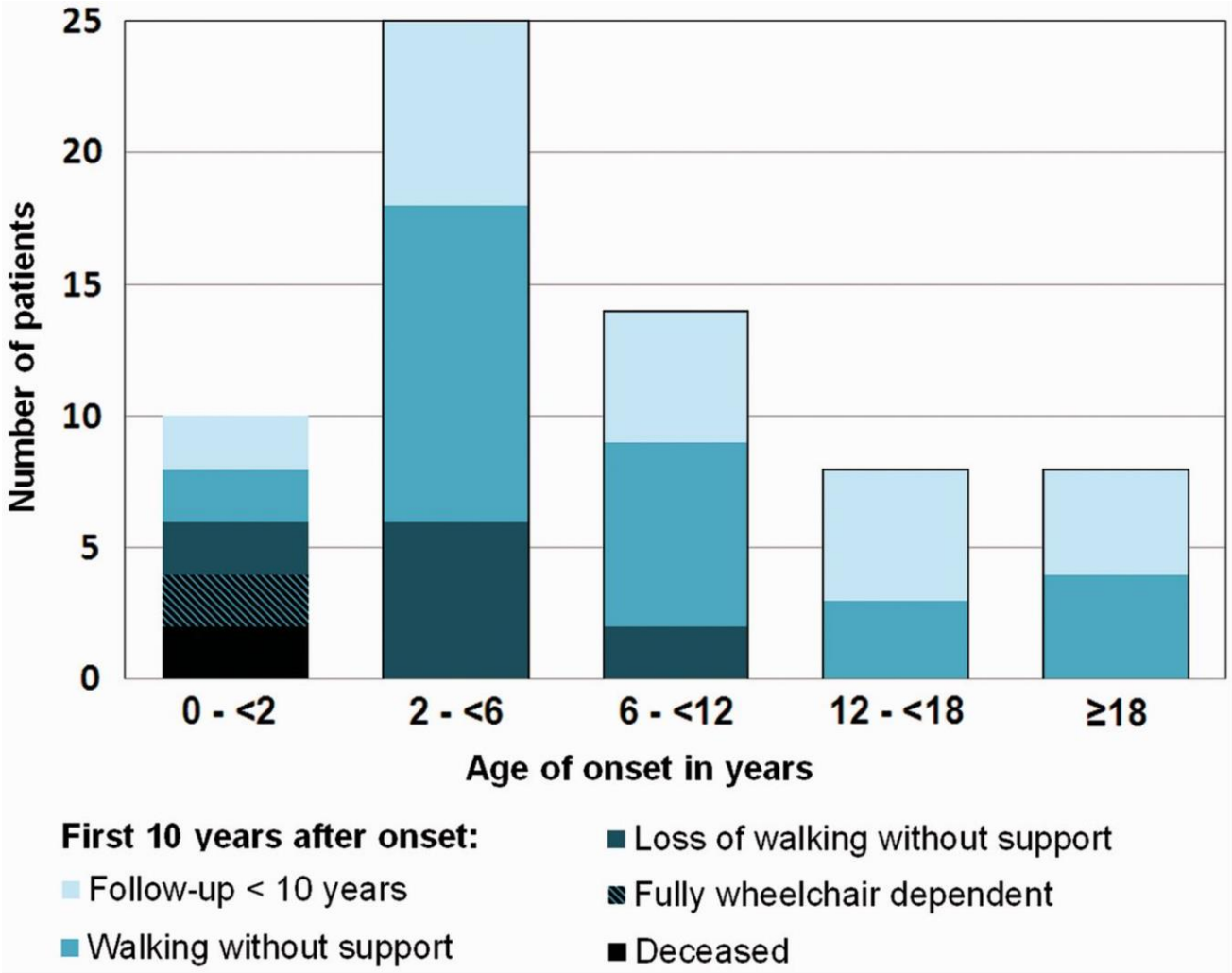
- Small head size at birth
- Low muscle tone at birth or early on
- Difficulty feeding and failure to thrive
- Motor and cognitive delays
- Often have severe epilepsy





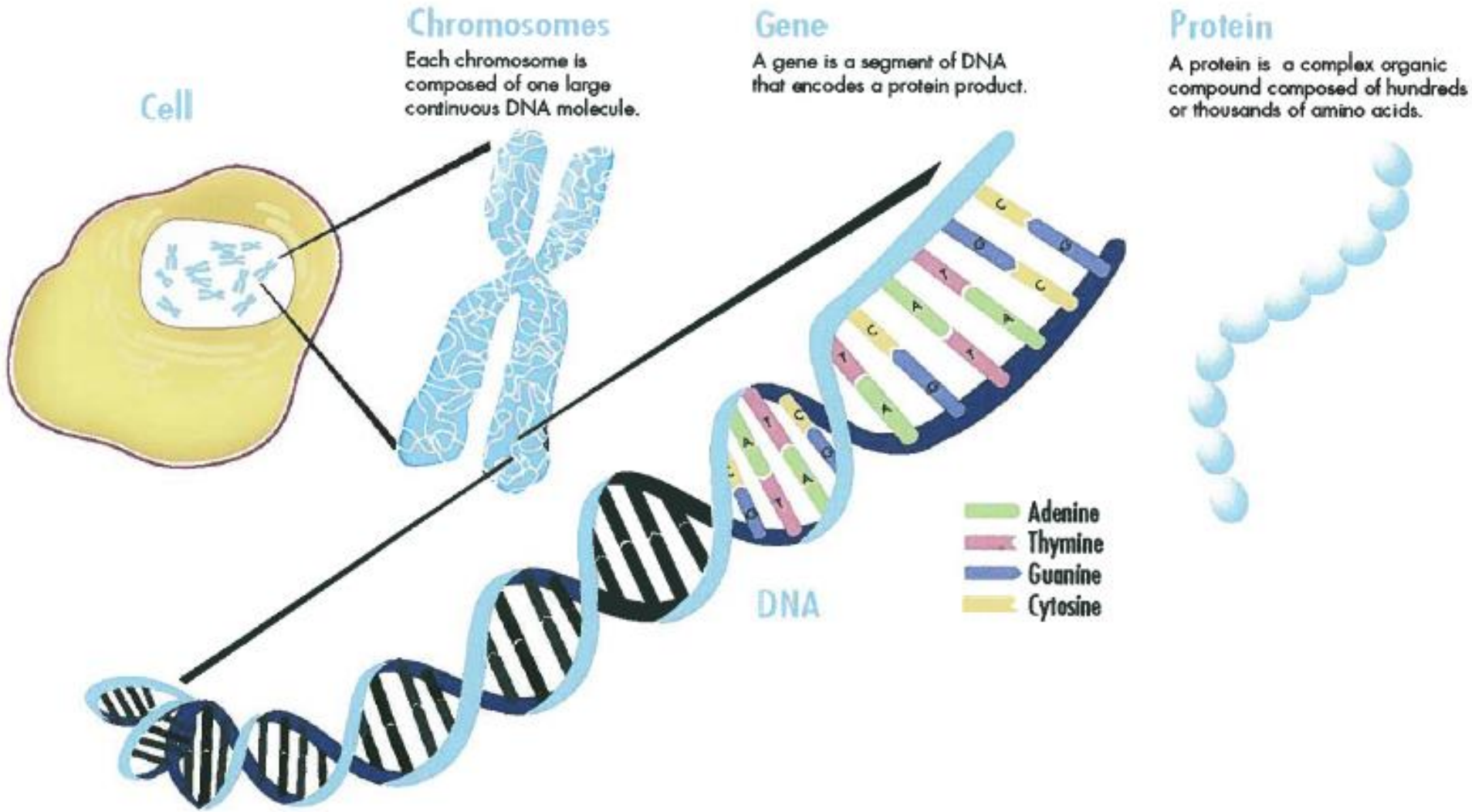
Progression of gait symptoms



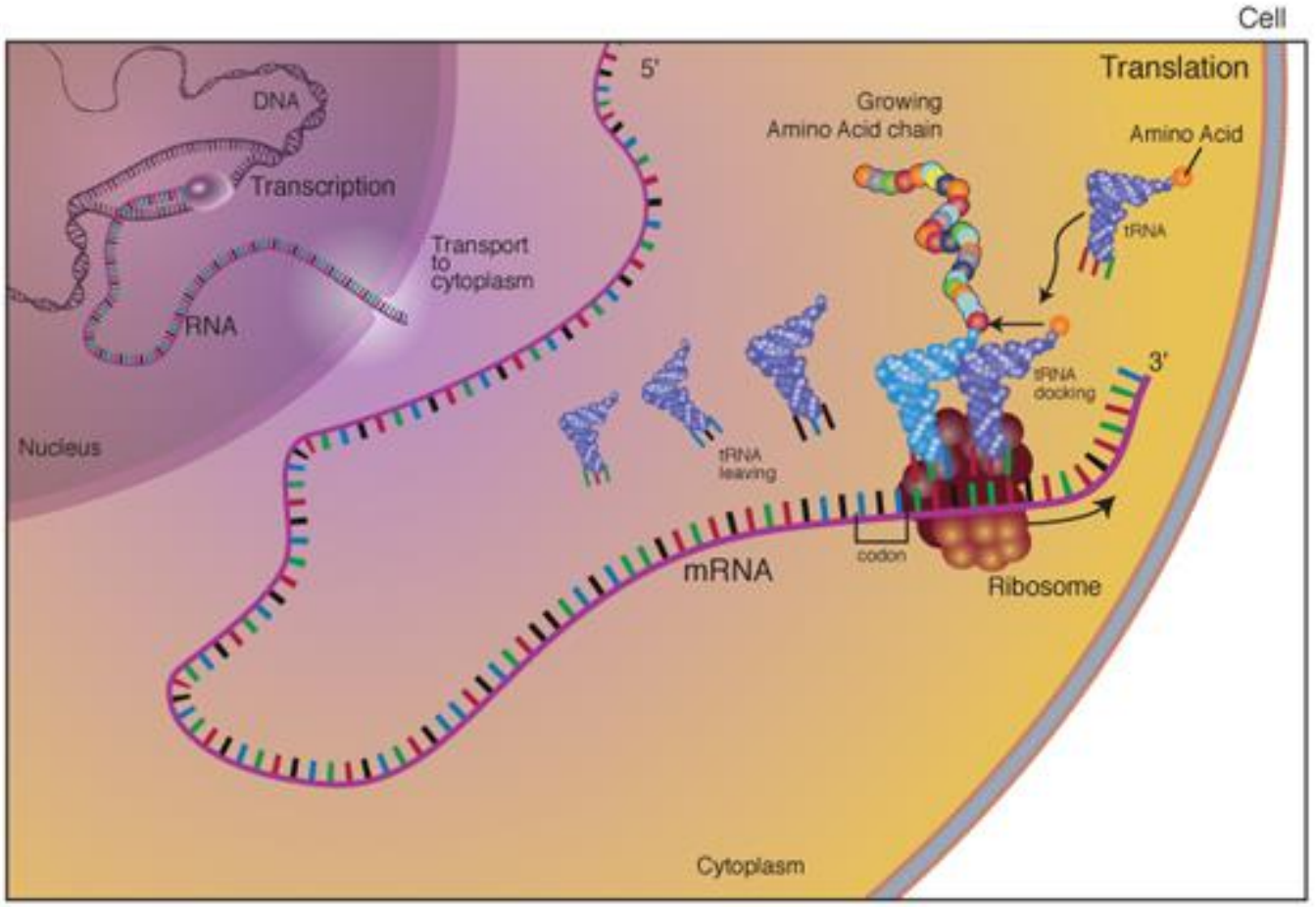


From Brain. 2014;137(4):1019-1029. doi:10.1093/brain/awu026

What is the basis of LBSL?



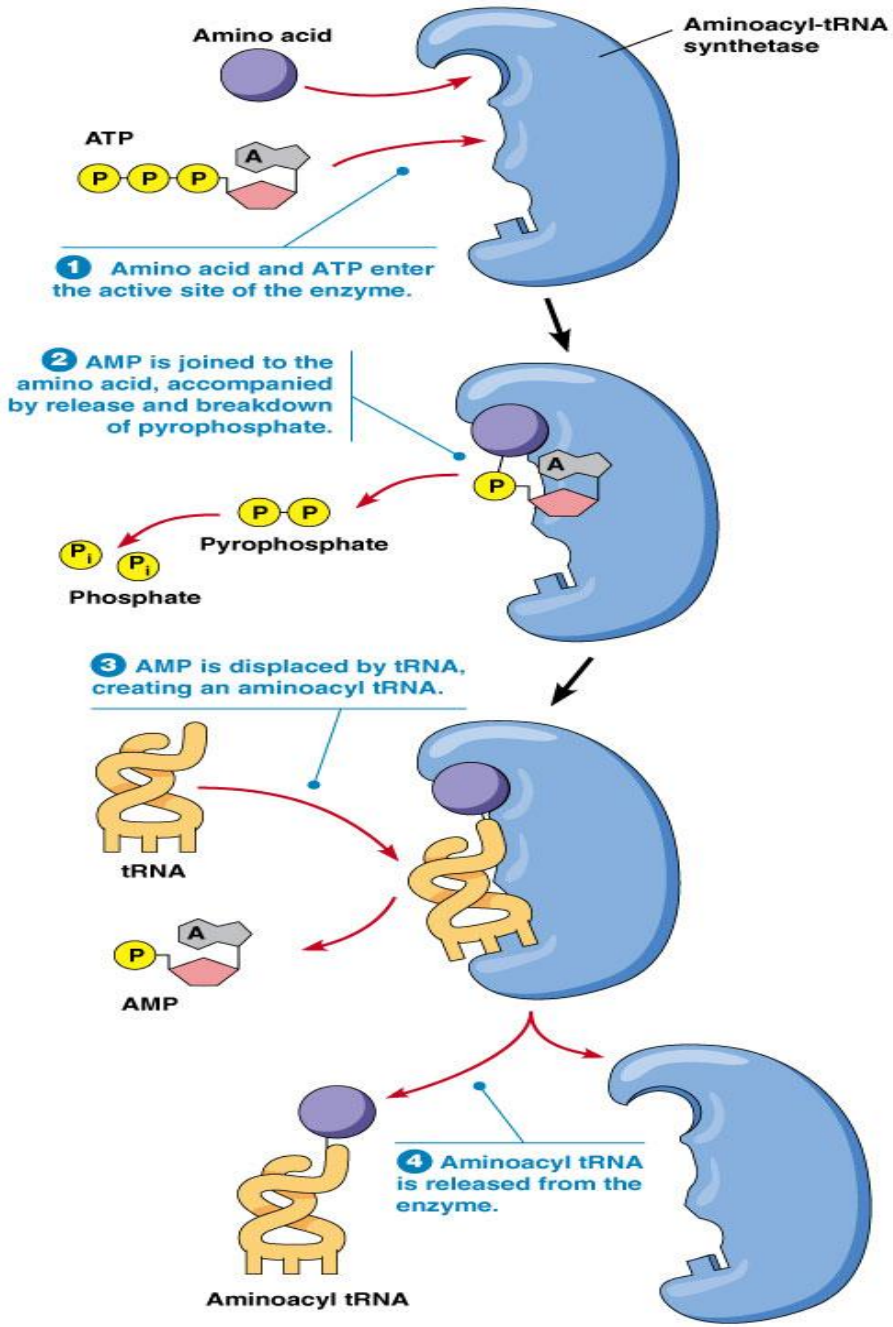
Translation- the way proteins are made.



https://www.youtube.com/watch?v=gG7uCskUOrA

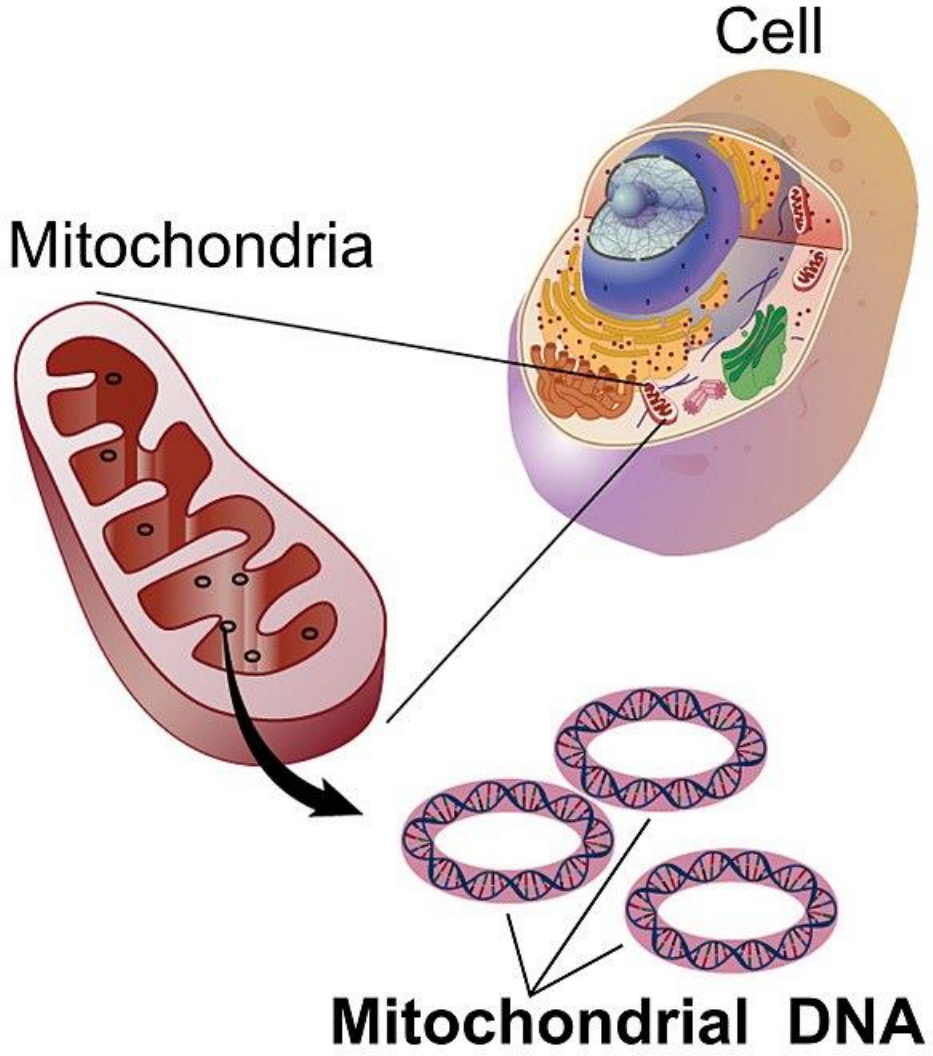
What are transfer RNA Synthetases?

- For each amino acid there is a
  - unique tRNA
  - Unique tRNA Syntethase



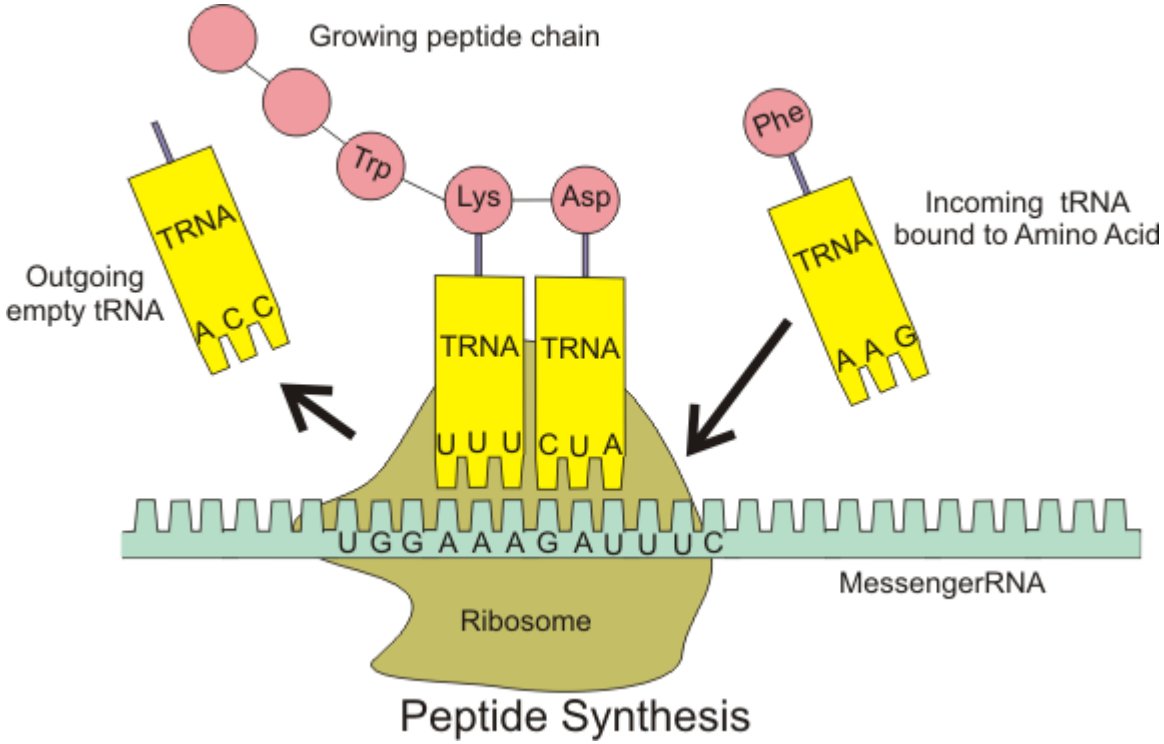
Mitochondria

- Energy factories
- Have their own DNA with 37 genes
- Have their own protein synthesis



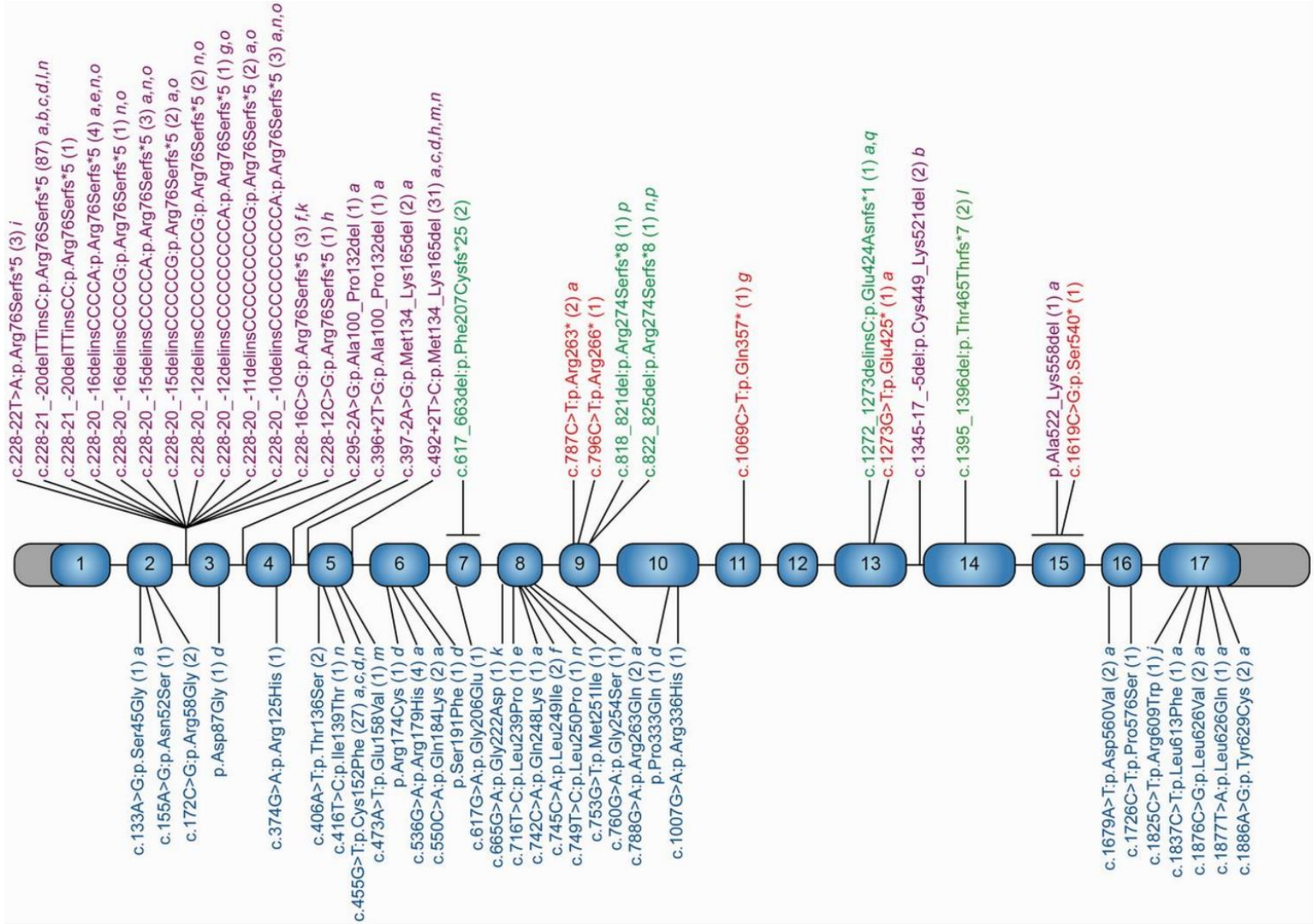
What is DARS2?

- *DARS2* encodes mitochondrial **aspartyl-tRNA synthetase**, the enzyme that attaches aspartate to the correct mitochondrial transfer RNA
  - Aspartyl-tRNA is necessary in the translation of mitochondrial messenger RNA into protein



What are *DARS2* mutations?

- Inheritance pattern is autosomal recessive van der Knaap 2010
- 60+ mutations Brain 2014



DON’T PANIC!

Is there mitochondrial dysfunction?

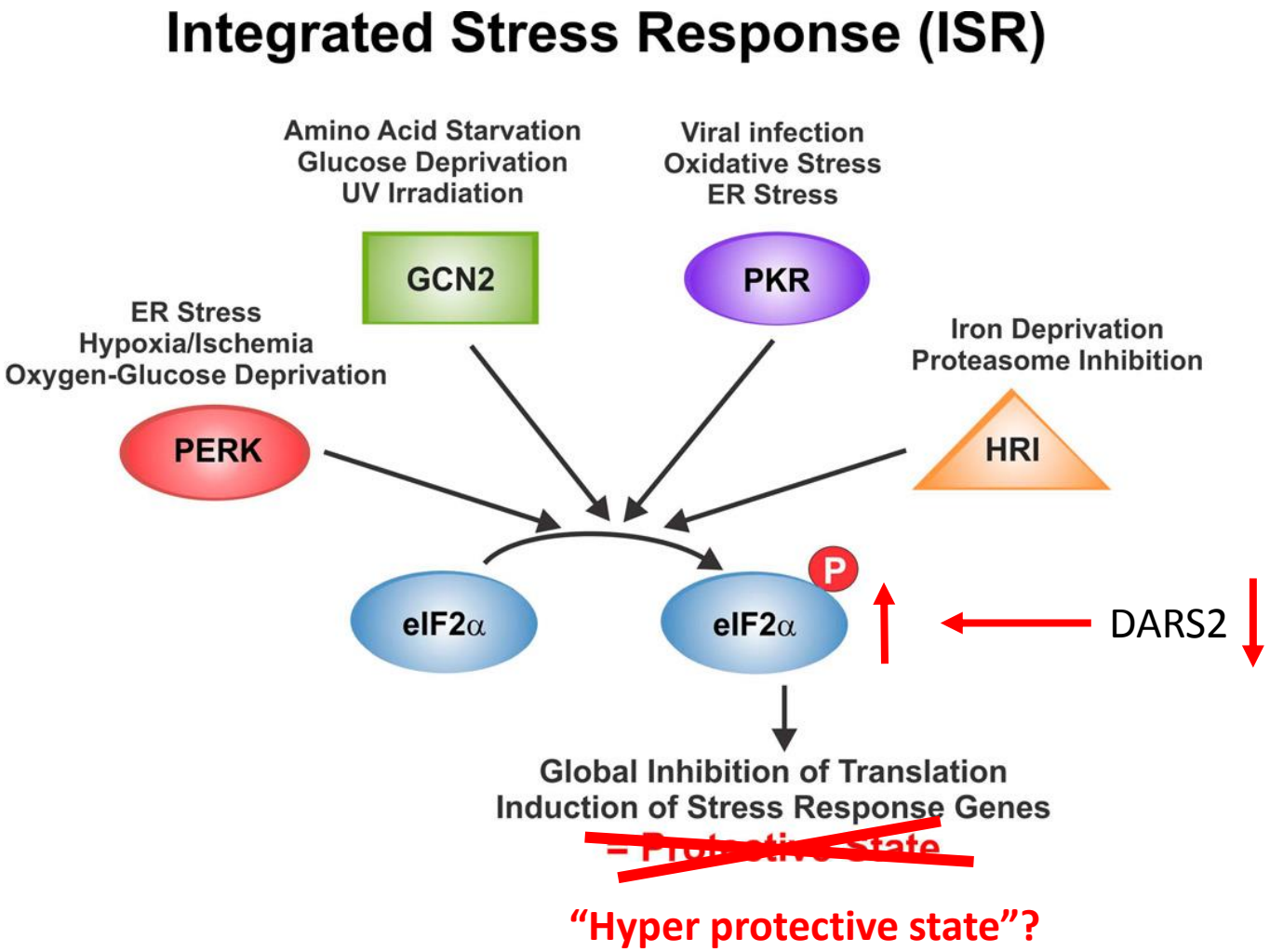
- Lactate in spinal fluid suggests impaired mitochondrial metabolism
- Complete absence of DARS2 in mouse tissues results in mitochondrial failure in those tissues.
- BUT patient skin and muscle cells seem to show normal mitochondrial function.

- Defect specific to brain cells?
- Is the DARS2 mutation in patients sufficient to cause stress to cells but not full mitochondrial dysfunction?

Integrated Stress Response (ISR)

New concept/pathway

Stressor to cells
→ISR activation
→Decrease in protein production
→Cell protection



Why do individuals with DARS2 mutations develop LBSL?

- Hypothesis 1:

Decreased DARS2 → decreased or impaired mitochondrial protein production → decrease mitochondrial function → oxidative stress and inflammation

- Hypothesis 2:

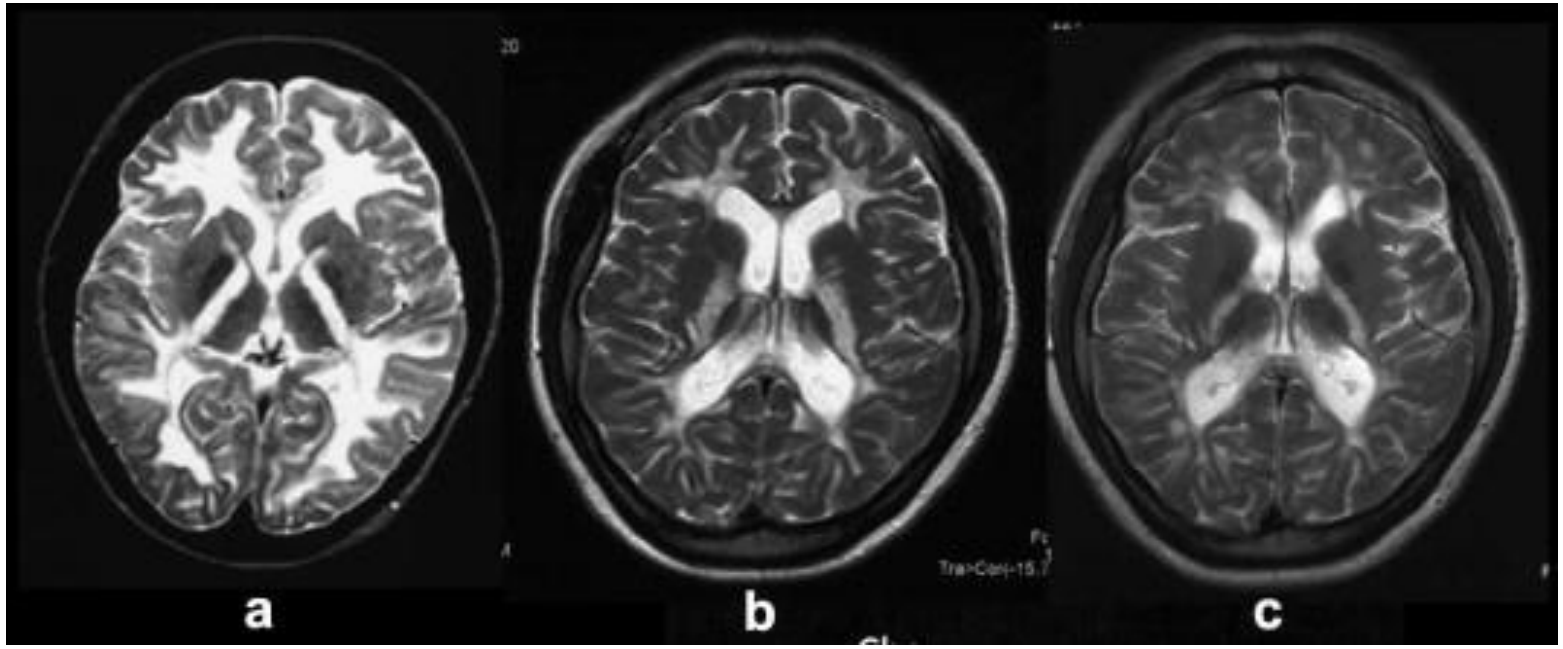
Abnormal DARS2 → dysregulation of integrated stress response → hyper suppression of protein production and delayed recovery

- Hypothesis 3 (my guess): Both of the above are contributors.

What happens to the MRI over time?

- Patients slowly get worse over decades often in episodic fashion
- Spontaneous recovery from acute episodes reported.
- MRI tends to get “better” on initial view
  - Decrease in inflammation?
  - Decrease in swelling of myelin?
  - Detailed look shows progression

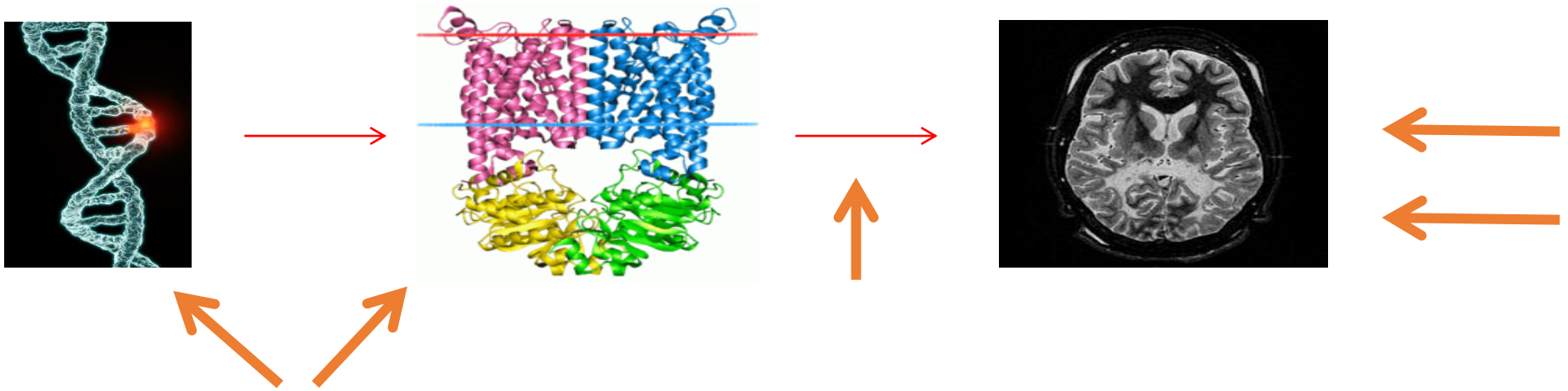
  In brainstem and spinal cord



What do we not know?

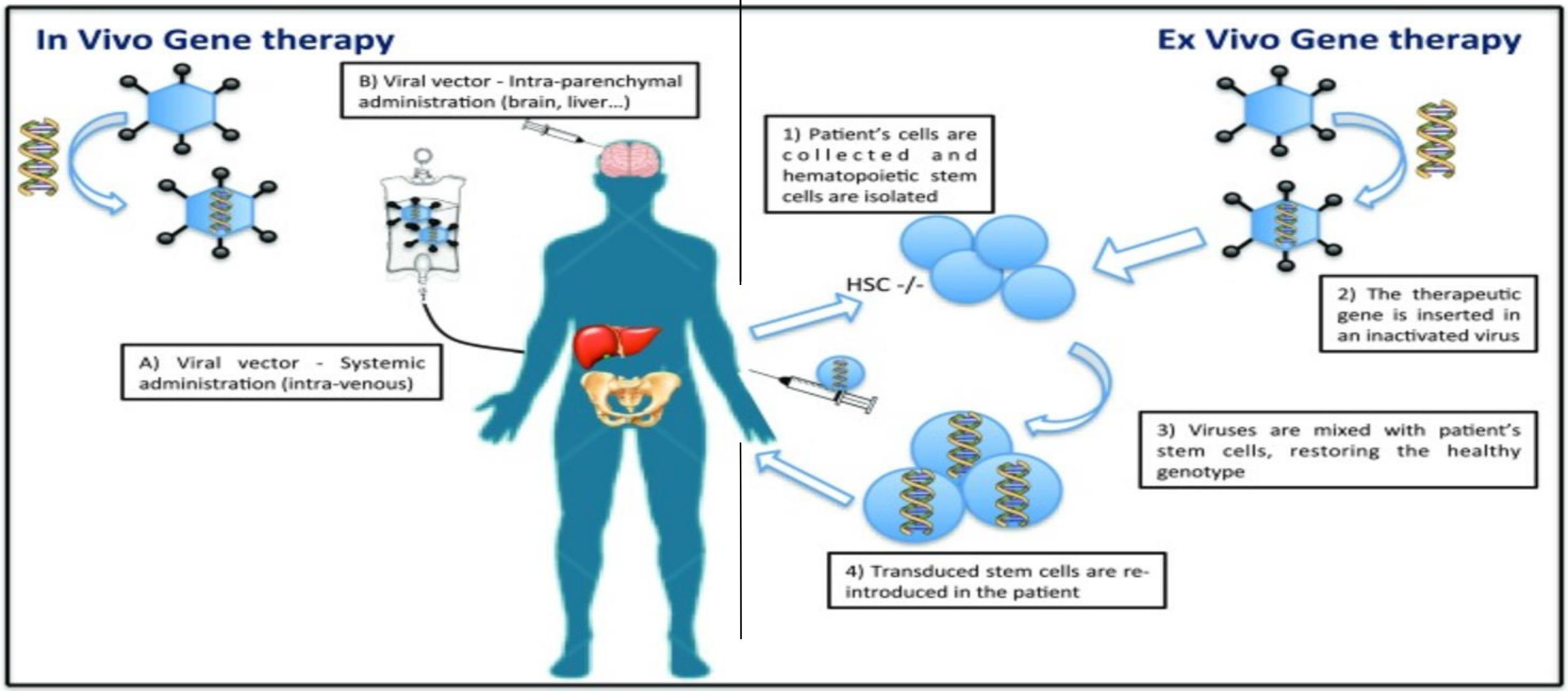
- Does the gene change predict severity and time of onset?
- What is the rate of progression of symptoms?
- Which symptoms get worse most?
- How does MRI change over time in larger group?
- What markers can be used to predict response to therapy?
- Is height and weight and bone growth affected?
- What are the triggers or risk factors for disease progression?
- What kind of cells are most affected?
- Which hypothesis is true in terms of mechanism of disease?

How to fix a Genetic Disease…



- Fix the gene/protein defect and prevent disease onset
- Arrest disease progression by small molecules that correct abnormal cell function
- Restore whatever has been damaged
- Overcome pathyphysiology

GENE DELIVERY

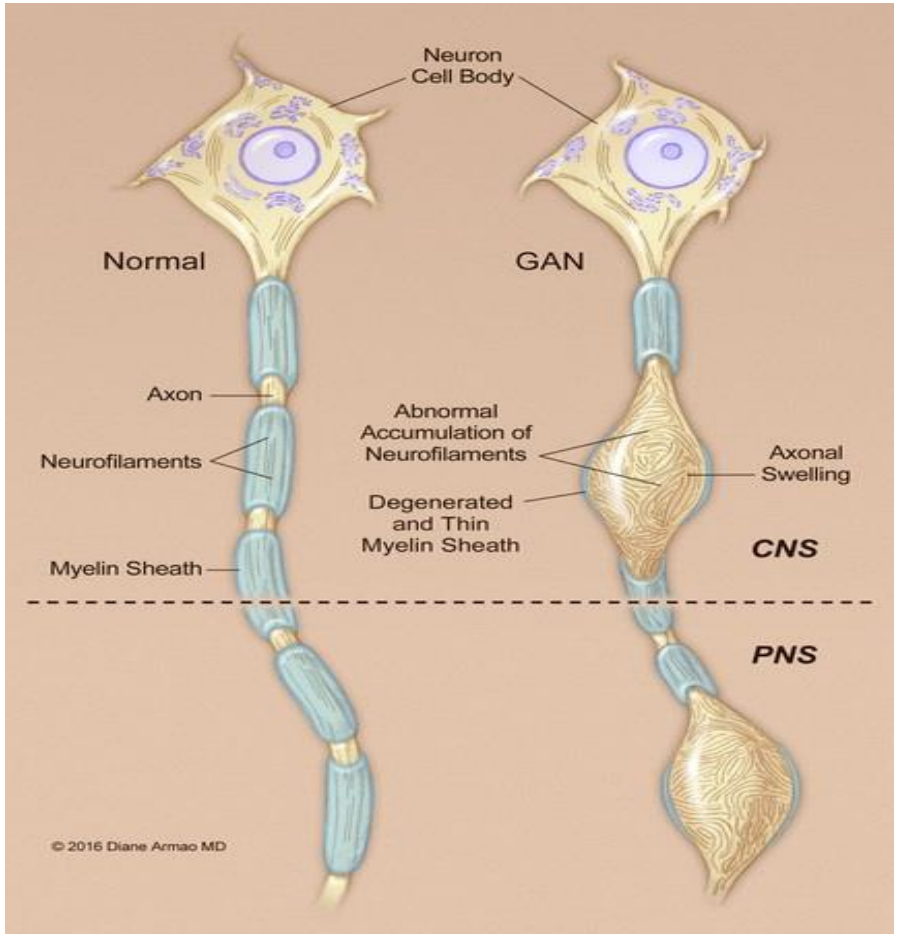


Challenges

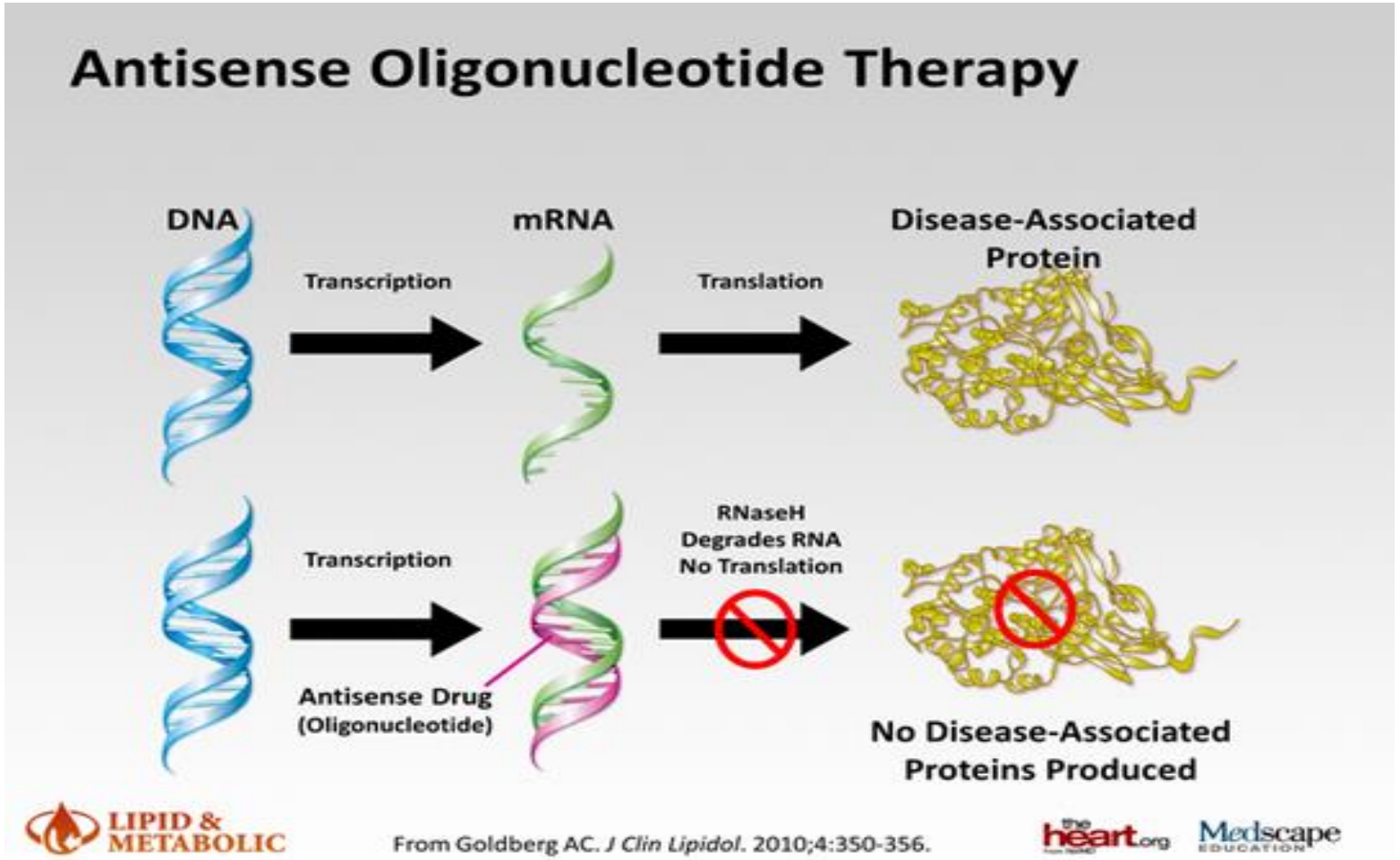
- How to deliver the virus to its target
- Systemic injection may result in
  - Expression of the gene in wrong places
    (eg. neuronal gene being expressed in heart)
  - Formation or presence of antibodies against the virus and protein product

Ongoing pediatric CNS AAV9 gene therapy Trial

- Phase I - Intrathecal Administration of scAAV9/JeT-GAN for the Treatment of **Giant Axonal Neuropathy**
- ClinicalTrials.gov #NCT02362438
- Patients with GAN > 5years of age
- Primary outcome: safety after 8 weeks
- Intrathecal injection of scAAV9 virus in 10-12 patients
- Preliminary Results presented suggest it is safe



- Antisense RNA prevent protein translation of certain mRNA strands by binding to them.
- Antisense DNA can be used to target a specific complementary RNA.

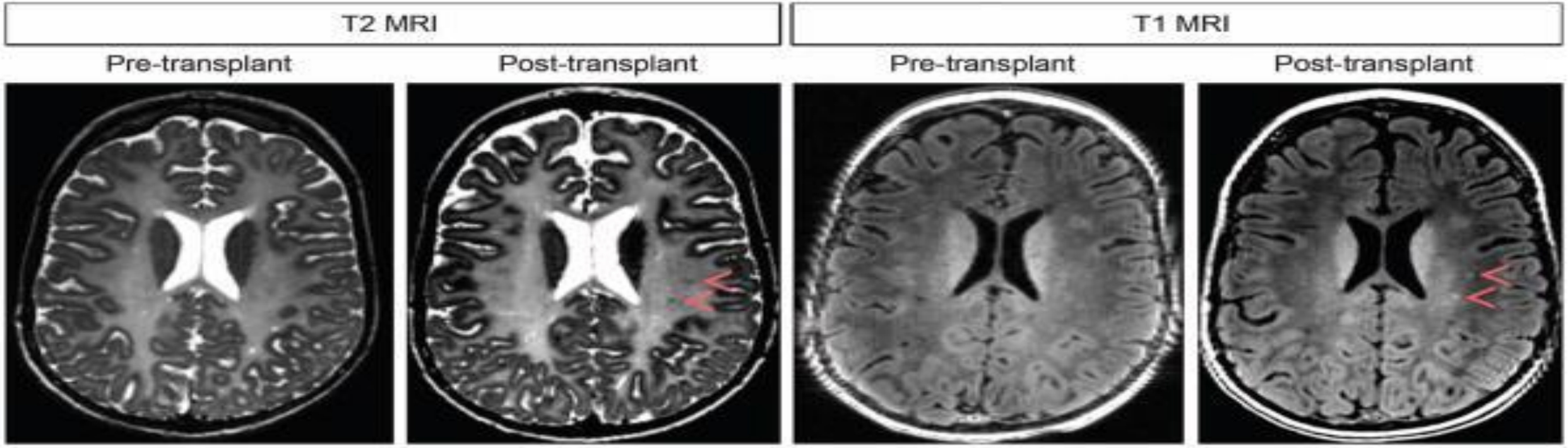


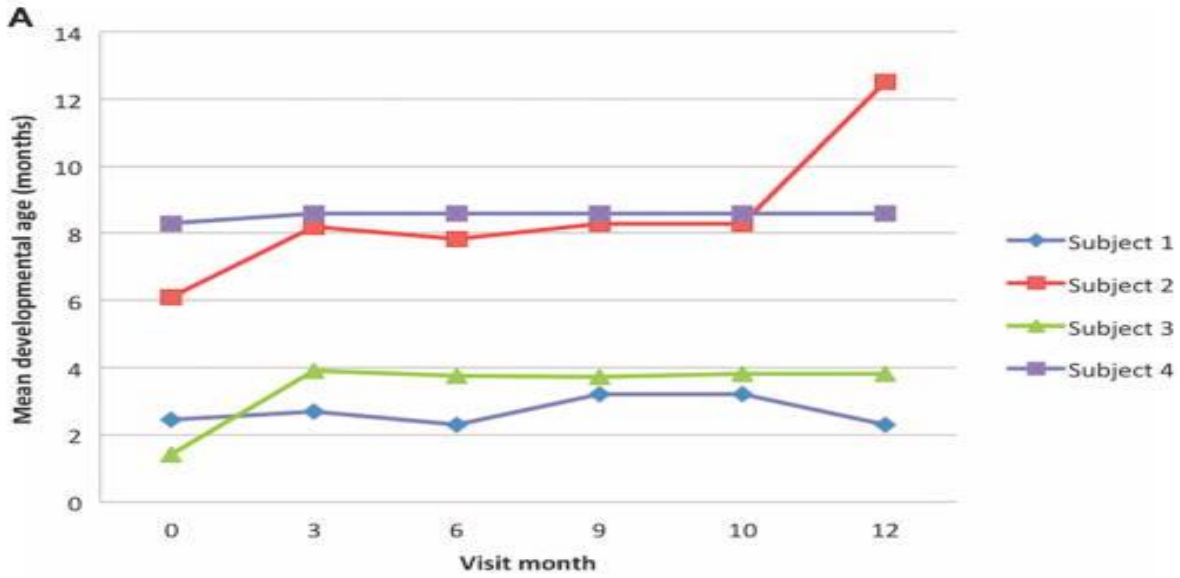
Limitations of ASO

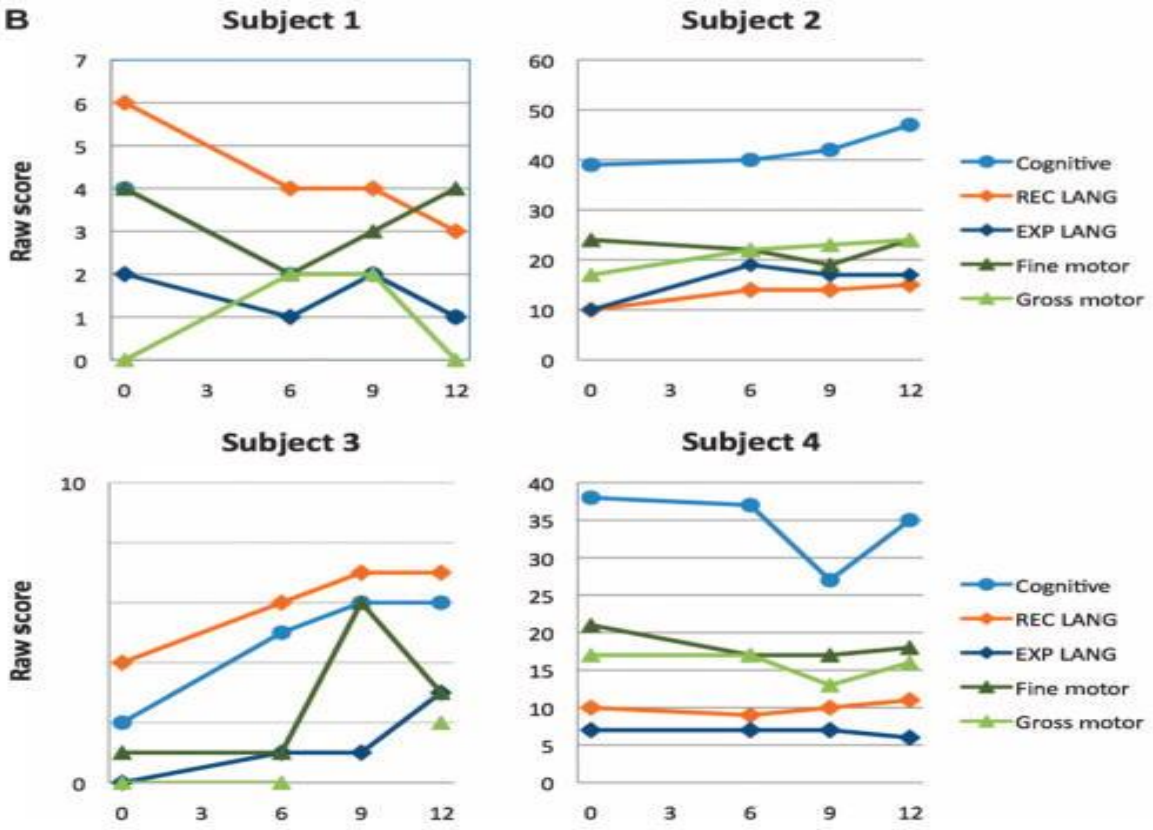
- Antisense agents have to be protected against nucleolytic attack.
- Large doses are required for therapeutic response.
- The difficulty in directing to a particular cells.
- The half-life in plasma is short.

Neural Stem Cell Transplantation in Patients with Pelizaeus-Merzbacher Disease

- Phase I study in 4 patients







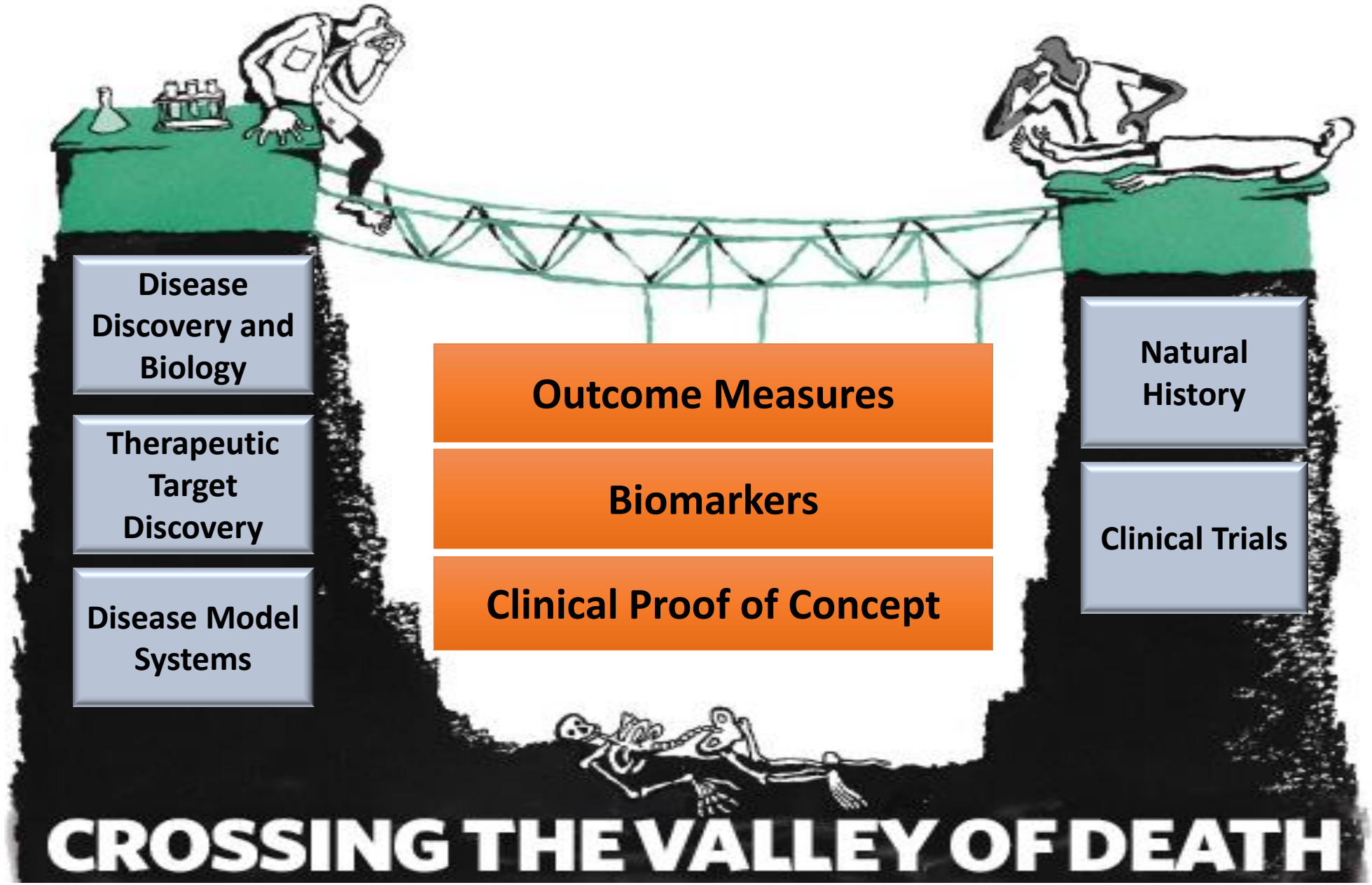
Challenges:

- Source of cells (if fetal) very limited
- Concern for malignancy
- Concern for graft versus host disease
- Immunosuppression

Sci Transl Med. Oct 10, 2012; 4(155).

Small Molecules that may slow disease progression

- Molecules that improve Mitochondrial function/metabolism in the brain?
- Molecules that improve inflammation in the brain?
- Molecules that normalize the Integrated Stress Response?


Disease Discovery and Biology
Therapeutic Target Discovery
Disease Model Systems
Outcome Measures
Biomarkers
Clinical Proof of Concept
Natural History
Clinical Trials
CROSSING THE VALLEY OF DEATH

THANK YOU!

ACureforEllie.org

National Institute of Neurological Disorders and Stroke

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

CPI Cerebral Palsy International Research Foundation Global Research for Developmental Brain Disorders

Run for ALD

brian's hope

Hunter's Hope