CRACKING THE CODE
CRACKING THE CODE
Houston, we have a problem.
LEUKODYSTROPHY

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**Myelin**

- **White Matter**
- **T1-Hypointensity**
- **T2-Hyperintensity**
- **High Signal**
- **LEUKODYSTROPHY**

**Corpus Callosum**

**Brain Stem**

**Cerebellum**

**Contrast**

**Differential Diagnosis**

- **Pelizaeus-Merzbacher Disease**
- **Salla Disease**
- **CSF Hypomyelination**
- **Hypomyelination**
- **Tay-Sachs Disease**
- **Fucosidosis**
- **Gangliosidosis**

**Atrophy**

- **Basal Ganglia**

**B12 Metabolism**

- **Consanguineous Marriage**

**MRI**

- **MRI T2-sag upper**
- **MRI T2-sag lower**

**Mag:** 2.4x

**ET:** 15
**TR:** 3020.0
**TE:** 93.0

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**MRI T1-Hypointensity**

**Hypomyelination**

**Sella Disease**

**High Signal**

**Differential Diagnosis**

- **Pelizaeus-Merzbacher Disease**
- **Salla Disease**
- **CSF Hypomyelination**
- **Hypomyelination**
- **Tay-Sachs Disease**
- **Fucosidosis**
- **Gangliosidosis**

**Atrophy**

- **Basal Ganglia**

**B12 Metabolism**

- **Consanguineous Marriage**

**MRI**

- **MRI T2-sag upper**
- **MRI T2-sag lower**

**Mag:** 4.5x

**ET:** 19
**TR:** 4270.0
**TE:** 117.0

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**MRI T1-Hypointensity**

**Hypomyelination**

**Sella Disease**

**High Signal**

**Differential Diagnosis**

- **Pelizaeus-Merzbacher Disease**
- **Salla Disease**
- **CSF Hypomyelination**
- **Hypomyelination**
- **Tay-Sachs Disease**
- **Fucosidosis**
- **Gangliosidosis**

**Atrophy**

- **Basal Ganglia**
Leukodystrophy comes from the Greek roots leuko (white), dys (lack of) and troph (growth).
Signals are unable to travel down this broken pathway.
electron micrograph
of myelinated axons
(white matter)
How Does Leukodystrophy Occur?

Leukodystrophies are genetic disorders.

Autosomal recessive disorders affect both boys and girls and require both parents to be carriers (heterozygotes). Carriers themselves have no disability, however on average there is a 25% chance of their children having the illness and a 50% chance of their children being carriers.

X-linked disorders are carried on the X chromosome, with only the mother being the carrier. Carriers themselves have no disability, however on average 50% of the daughters of a woman who is a carrier will also be carriers and 50% of the sons of a woman who is a carrier will have the disorder.
MRI / Genetics Diagnosis

An MRI-based approach to the diagnosis of white matter disorders.
Raphael Schiffmann and Marjo S. van der Knaap

Dr Richard Leventer
Paediatric Neurologist
Royal Children's Hospital
Melbourne Australia

Professor Marjo van der Knaap
Paediatric Neurologist
VU Medisch Centrum
Amsterdam Netherlands
44 times around the Earth
4.6 times from the Earth to the Moon
An MRI-based approach to the diagnosis of white matter disorders.

Raphael Schiffmann and Marjo S. van der Knaap
An MRI-based approach to the diagnosis of white matter disorders.
Raphael Schiffmann and Marjo S. van der Knaap
Although children can be diagnosed with a Leukodystrophy based on imaging alone, >50% of variants of this debilitating condition remain genetically unclassified offering little hope of treatment, an unknown future and an almost certain tragic outcome.
11,481 Single Nucleotide Variations
175 Insertions
206 Deletions
7,814 Heterozygous
4,084 Homozygous
5,726 Genes
Familial Trio Genome Analysis

42
Familial Trio Genome Analysis

Step 1: Mapping, mate joining and alignment

Step 2: Filtering (sort, duplicate removal, merge and index)

Step 3: Realignment and Quality Score Assessment (GATK)

Step 4: Identification of potentially damaging SNPs

A: PolyPhen
B: SIFT
C: Mutation Taser

Prediction of pathogenicity

Candidate Genes

Dr Ryan Taft
Senior Research Fellow
University of Queensland
Brisbane Australia
Familial Trio Genome Analysis

Filter out variants common to Massimo and either Mum or Dad (non pathogenic)
Screen for compound heterozygotes (predictive pathogenic combinations)
<table>
<thead>
<tr>
<th>Family Member</th>
<th>Inheritance</th>
<th>Rationale</th>
<th>Variant ID</th>
<th>Position</th>
</tr>
</thead>
</table>
n = 1
Validation | Candidate Gene

How do we prove DARS variants are causal?

- Option 1 - Knock In / Knock Out Mouse Model
  - incredibly costly  $250,000
  - time-consuming  3 years
  - uncertain result  it’s still a mouse

- Option 2 - Find a cohort of patients with the same presentation (phenotype)
  - variants in the same gene and / or pathway
  - easier said than done
MDBP is an established bioregistry of almost 700 registered patients. All have detailed clinical information - MRIs and genetic material available. Most have genetic material available from both biological parents.

Collaborating clinicians identified several “Massimo Like” patients:

- Four families with one affected child
- One family with two affected children
“After 1,161 days we achieved a confirmed diagnosis for Massimo and in the process discovered a new disorder. Both children in a family of five from the United States were confirmed as having the same genetic variations, as were several from Europe, and potentially many, many more from across the world. What was more exciting than achieving the diagnosis itself was discovering some of these children are in their teens and stable. Massimo is no longer alone and now we have hope.”
The McLaughlin Family

Affected and carrying compound heterozygous mutations in DARS

Unaffected and not carrying a compound heterozygous mutation in DARS
In addition to Massimo, 9 more children were identified with mutations in the DARS gene.

This validated the diagnosis and identified a disease entirely new to medicine called Hypomyelination of the Brain stem and Spinal cord leading to Leg spasticity (HBSL).

The research team was published in the American Journal of Human Genetics Volume 92 / Number 5 / 2nd May 2013.
MASSIMO EFFECT
The Foundation

Promote the prevention, diagnosis and treatment of childhood leukodystrophies.

Accelerate the discovery of novel genetic variations responsible for childhood leukodystrophies and to translate these findings into clinical trials and treatments.
When a disease is perceived as rare the level of attention and funding it receives is almost non-existent. However, childhood Leukodystrophies, whilst individually rare, appear to be not altogether uncommon. In fact these conditions may affect up to 1 in 3,000 births, a prevalence not dissimilar to Cystic Fibrosis, yet their existence remains almost unknown.
If we can reduce the number undiagnosed cases to less than 10% within five years and show that a common delivery platform, known as a vector, can treat multiple disorders the game suddenly changes and will drive public and private investment into research.
JOIN OUR MISSION
TO END CHILDHOOD LEUKODYSTROPHIES AND WIN A TRIP INTO SPACE
A giant stride for good causes
Runners raise $1.8m for charity
Scientific crew

Brainy Bunch