



## I. The Campbell Family Background

Aaron and Emily Campbell and their five children have lived all over the world calling places like South America, South Africa and India home. In 2011, the family began their journey in conquering another challenge. Victoria, the Campbell's oldest daughter, began struggling in school accompanied by coordination issues. An MRI revealed that Victoria suffered from brain damage due to a genetic disorder called juvenile onset metachromatic leukodystrophy (MLD). A second daughter, Madelena, was diagnosed a week later. After genetic testing of the remaining three children, the youngest son, Ike, was also diagnosed while Emma and Eli were determined to be carriers of the disorder.

Sadly, on September 7, 2014 Victoria lost her courageous battle to the ravages of MLD.



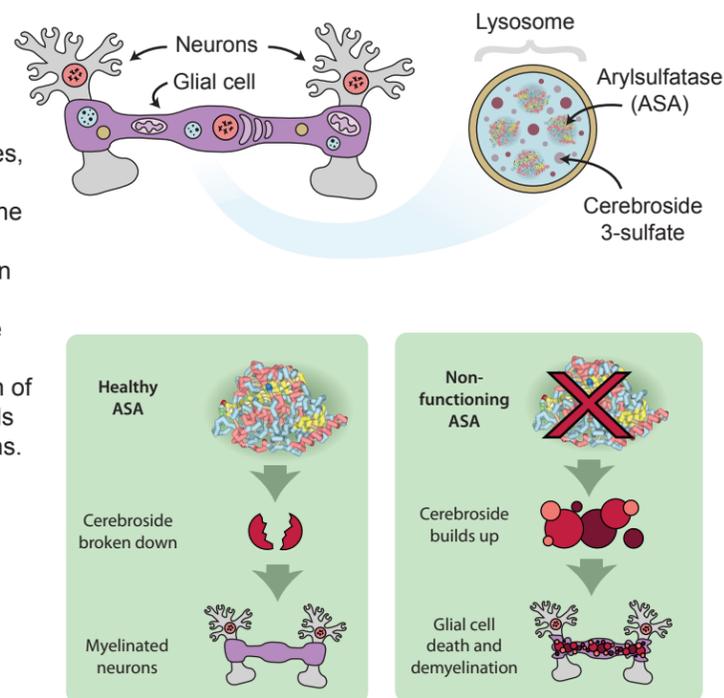
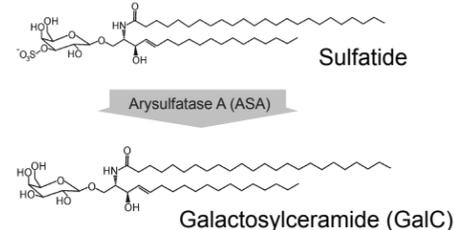
The Campbell family, Victoria, Emily, Aaron, Madelena, Emma (back), Eli, Ike and their dog Ginger, (front) pose for a portrait at their home in Orem, Utah on Sunday, Jan. 26, 2014. SPENSER HEAPS, Daily Herald

## II. Metachromatic Leukodystrophy

Metachromatic leukodystrophy is an autosomal recessive genetic defect in the ARSA gene that occurs once in every 40,000 births. The disease name translates to meta – change, chromatic – color, leuko – white matter, dystrophy – degeneration. A degeneration of white matter in the nervous system results in a color that should not be there upon staining of the tissue. Three types of MLD – late infantile, juvenile and adult onset have been identified. The type of MLD correlates with the genetic defect and usually remains consistent within a family. Loss or miscommunication between the nerves accounts for the loss of acquired functions, paralysis, blindness, seizures and eventually death.

## III. The Role of Arylsulfatase A in Metachromatic Leukodystrophy

Arylsulfatase A (ASA) is a lysosomal enzyme responsible for metabolizing sulfatides, sulfate-containing lipids found in the myelin sheath that insulates neurons. Mutations in the ARSA gene encoding ASA can result in a defective enzyme, leading to the accumulation of sulfatides in the lysosomes of myelin producing glial cells – oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. Accumulation of sulfatides leads to the death of these glial cells and eventually to the demyelination of neurons.

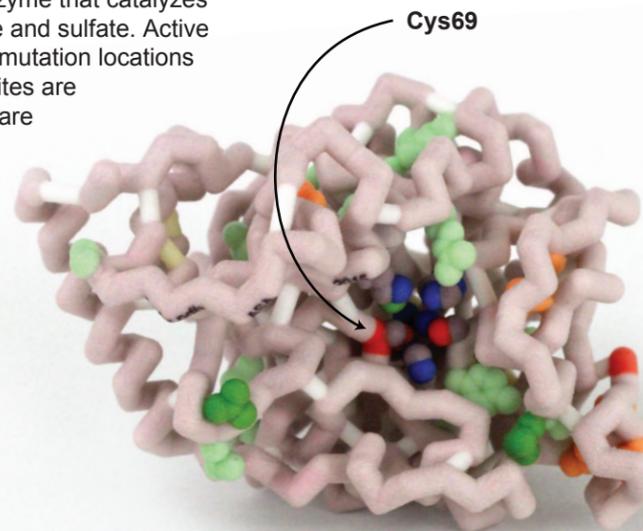
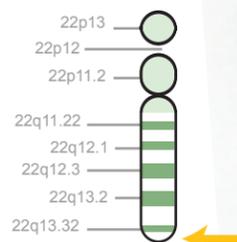


## IV. Arylsulfatase A – Based on 1e1z.pdb

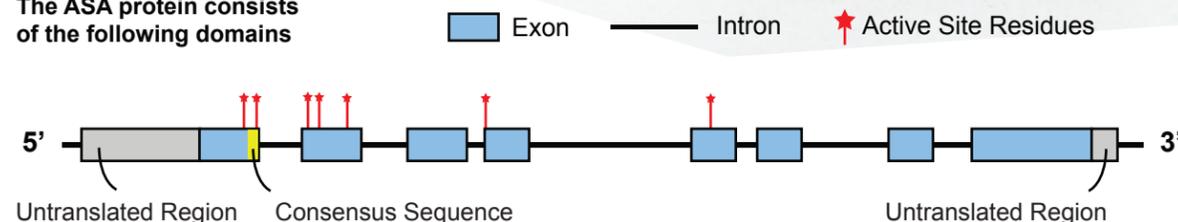
ASA is a 507 amino acid long lysosomal enzyme that catalyzes the breakdown of sulfatides into cerebroside and sulfate. Active site amino acids are colored CPK, selected mutation locations are colored mint green, common mutation sites are highlighted dark green, and disulfide bonds are highlighted yellow.

The ARSA gene is located on the long (q) arm of chromosome 22 at position 13.33.

Or, more precisely, from base pair 50,622,753 to base pair 50,628,172.

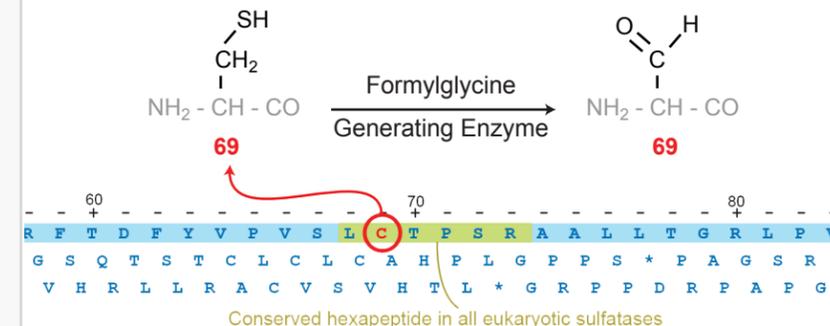


The ASA protein consists of the following domains



## V. Post-translational Modification

Eukaryotic sulfatases carry an alpha-formylglycine residue that is essential for activity and is located within the catalytic site. Cysteine 69 is post-translationally modified to Cα-formylglycine.



## VI. Treatment

Currently there is no cure for metachromatic leukodystrophy. Research is underway pursuing several new therapies.

1. Stem cell (SCT) or bone marrow transplant (BMT) is the only treatment at present. This therapy slows further deterioration of the myelin sheath by replacing marrow that can produce ASA. The transplant does not reverse the damage that has already incurred and is very hard on the MLD patient.

2. Active clinical trials for MLD include:

- a) enzyme replacement therapy where the malfunctioning enzyme ASA is replaced by a man-made recombinant enzyme injected into the MLD patient.
- b) substrate reduction therapy where instead of increasing the enzyme levels, therapy is focused on reducing the amount of sulfatide produced by the body.
- c) gene therapy with hematopoietic stem cell transplant uses the patient's own genetically modified hematopoietic stem cells to increase ASA production to 10-15 times the normal rate.
- d) intracerebral gene therapy based on the intracerebral injection of ARSA cDNA coding for ASA into the brain of patients.

## References

- <https://www.facebook.com/TheChoiceLife>
- <http://www.mldfoundation.org/mld-101-what.html>
- <http://ghr.nlm.nih.gov/gene/ARSA>

Wenger et al. (2013). Sixteen Novel Mutations in the Arylsulfatase A Gene Causing Metachromatic Leukodystrophy. *Gene*. 530: 323-328/