HSAN1:
Hereditary Sensory and Autonomic Neuropathy Type 1

Deater Foundation, Inc.

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What is HSAN1?

Hereditary Sensory and Autonomic Neuropathy Type 1

- **Dominantly inherited peripheral neuropathy**
- **Characterized by severe sensory loss (ie. temperature, pressure, pain)**
- **Starts in the extremities, usually in the feet first**

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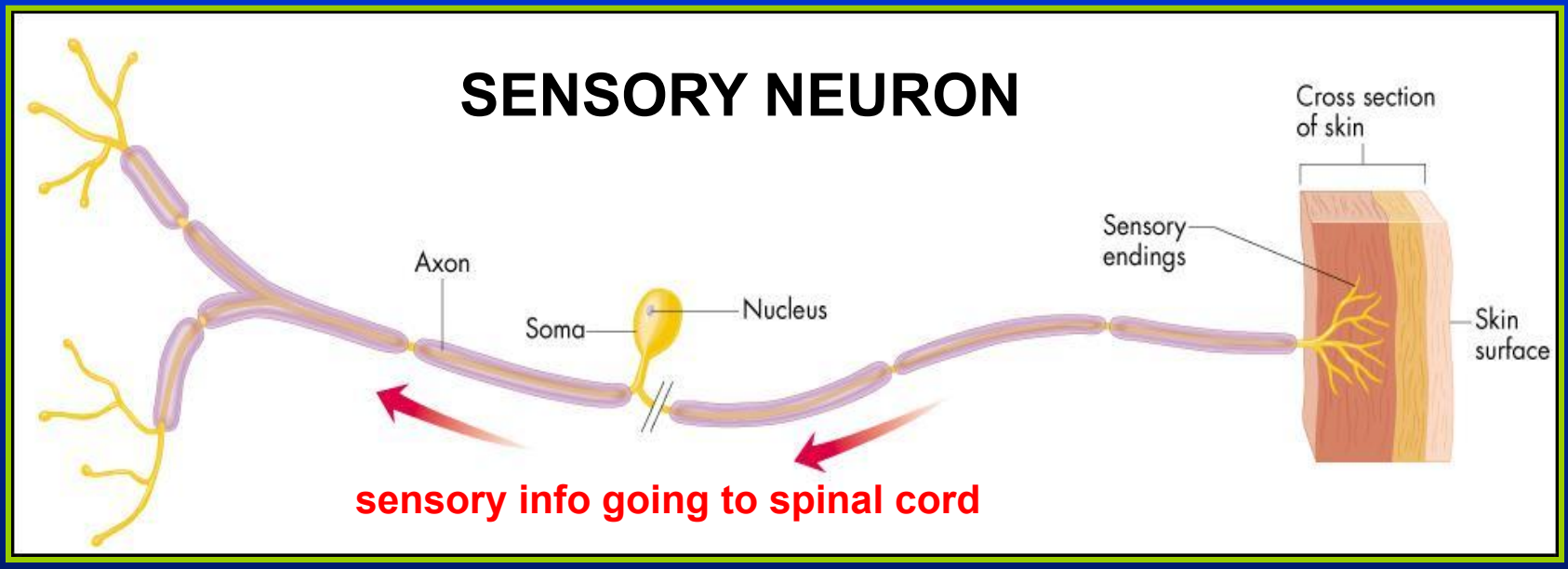
Symptoms of HSAN1:

- **Loss of sensation (pain, temperature, pressure) in the feet and hands**
- **Loss of reflexes in hands and feet**
- **Painless skin injuries that lead to:**
  - **chronic ulcers**
  - **osteomyelitis (bone infection and inflammation)**
- **Peripheral muscle wasting and weakness**
- **Lightening pains (sharp or shooting pains)**
- **Amputations**
- **Motor impairment**

Onset of symptoms usually becomes noticeable in the late teens to 2nd decade of life

What Normally Happens to Relay Sensory Info?

Sensory neurons carry information about the environment, such as pressure, touch, temperature, and pain to the spinal cord. From there, signals get carried to the brain to tell the body what sensation is being detected.



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In people with HSAN1, loss of sensory neuron function eventually leads to a loss of sensory perception

Since the neurons responsible for relaying the messages received in the skin are no longer present or functioning, no messages (ie. pain, pressure, temperature) can be transmitted

What Causes HSAN1?

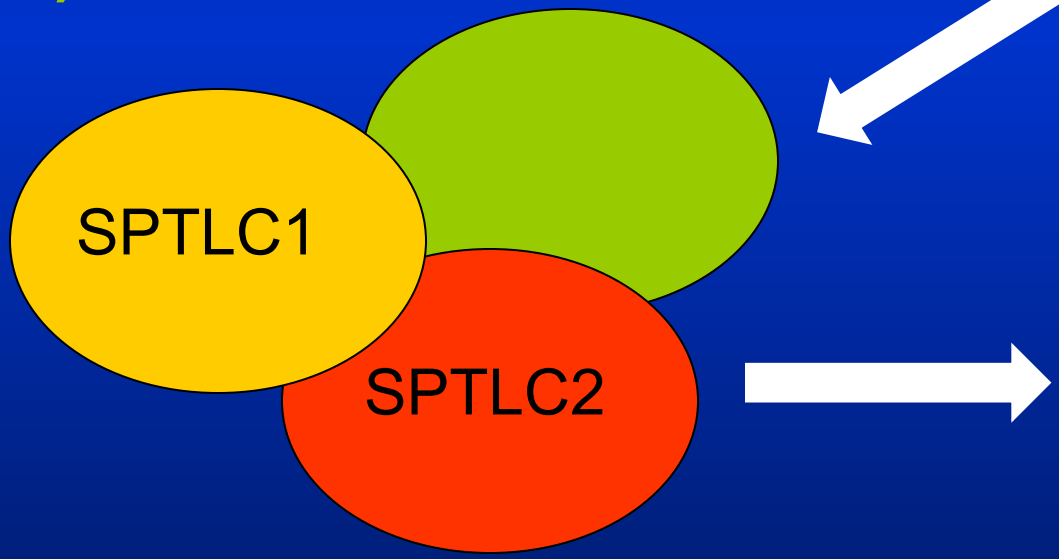
HSAN1 has been found to be caused by mutations in the genes, *SPTLC1* and *SPTLC2*

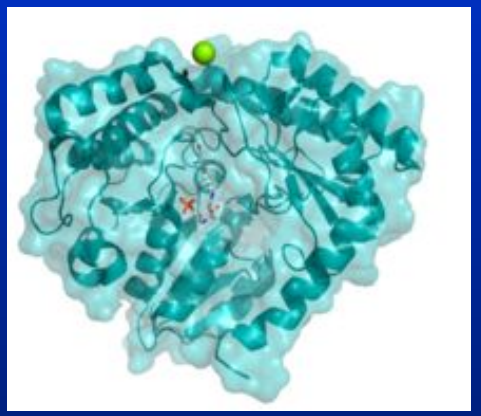
Genes are pieces of DNA (genetic instructions for making living organisms)

Genes contain information to make specific **Proteins** (ie. enzymes)

What Do These Genes Do?

SPTLC1 **and** ***SPTLC2*** **encode two subunits of the enzyme, Serine Palmitoyltransferase (SPT)**





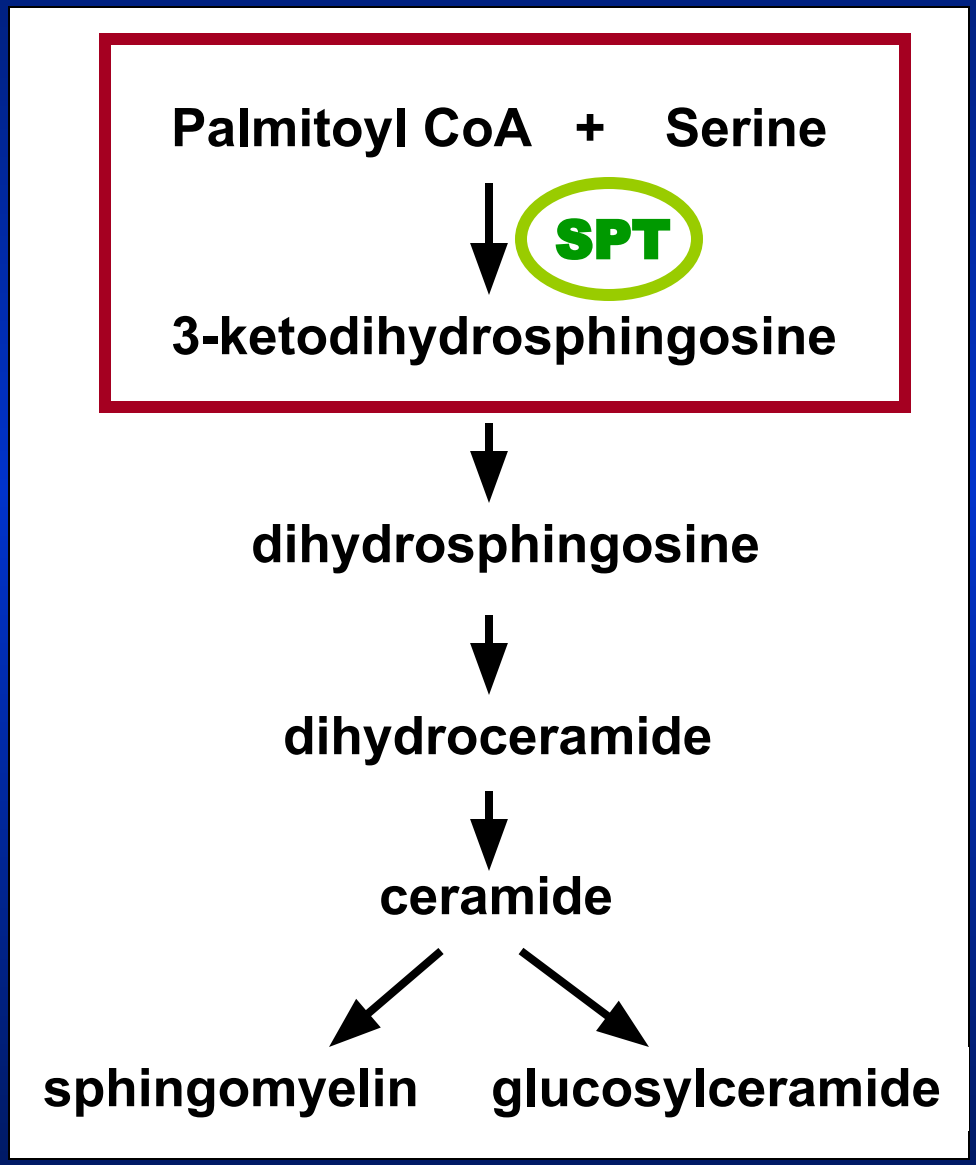
Serine Palmitoyltransferase (SPT)

What Does SPT Do?

SPT completes the first and rate-limiting step in the production of **sphingolipids**
(see circle in diagram)

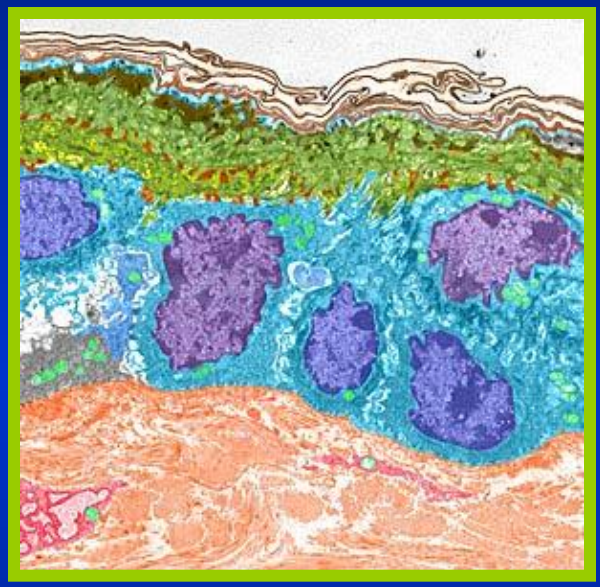
(sphingolipids)

Pathway for Sphingolipid Production:

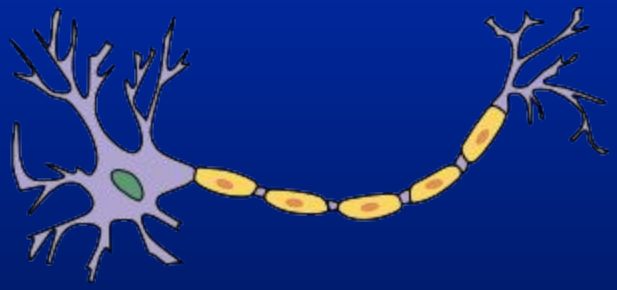


What are Sphingolipids?

Sphingolipids play an important role in cell structure and signaling…

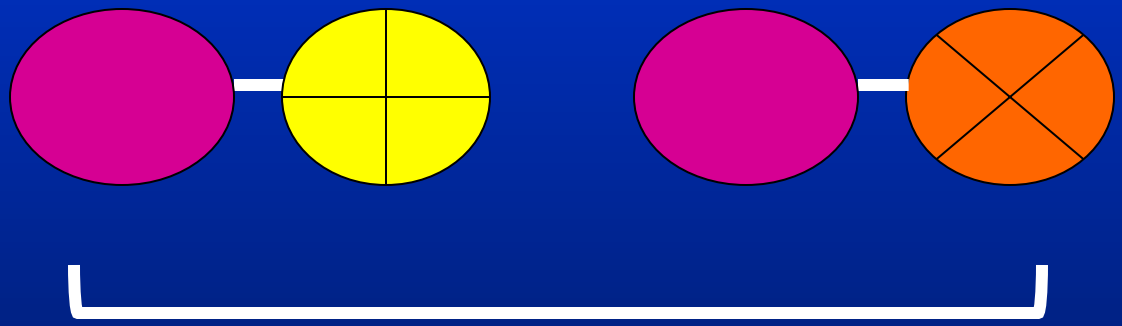


…especially in neurons



What Happens in HSAN1?

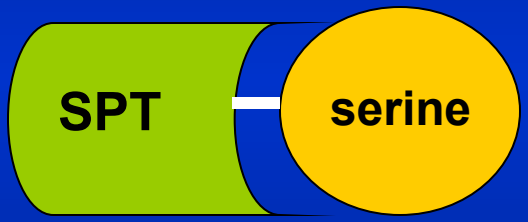
Based on findings in humans and mice, HSAN1 is thought to be caused by the accumulation of two atypical deoxysphingoid bases (DSBs)



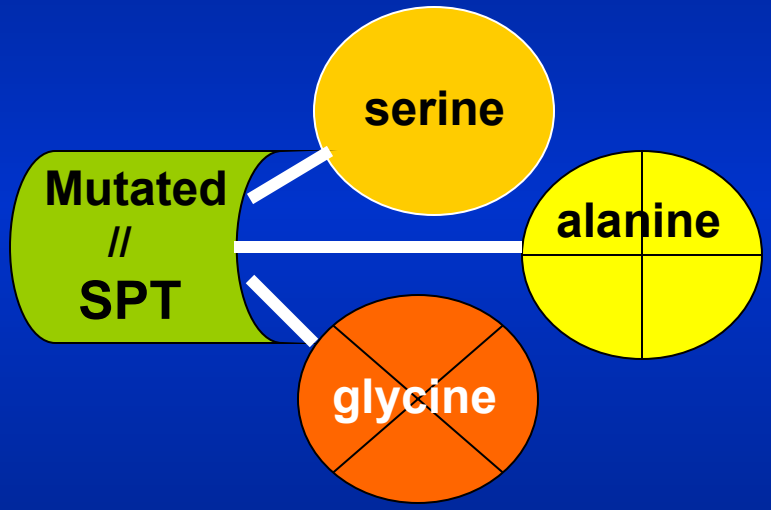
DSBs

What Causes DSBs?

DSBs are formed by an alteration in SPT enzyme substrate specificity:



Normal SPT prefers to pick up the amino acid, serine, during the first step of sphingolipid synthesis

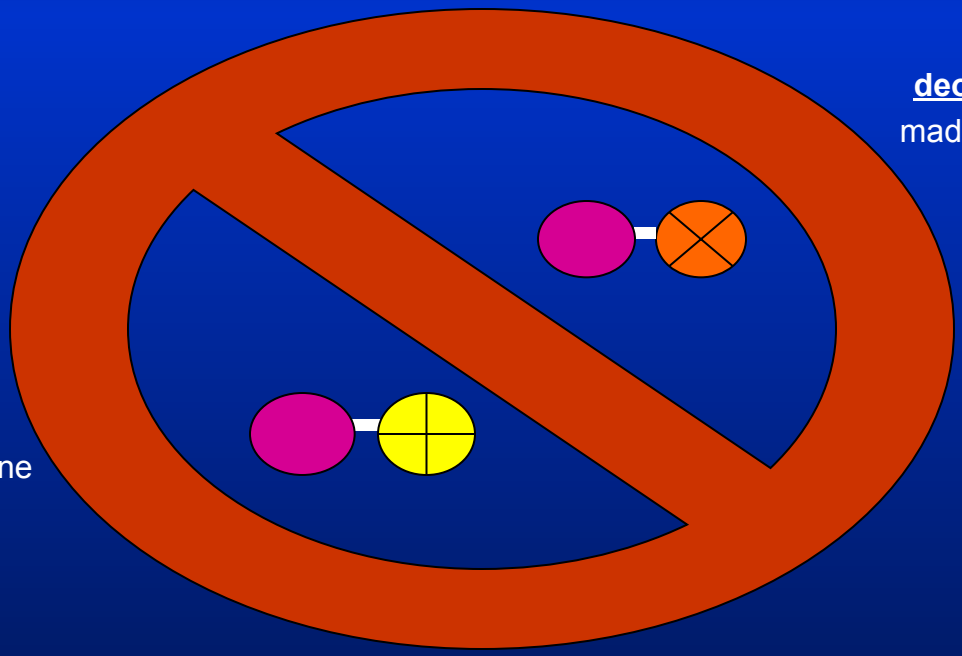


Mutated SPT picks up other amino acids, like glycine and alanine, in addition to serine

The Result?

The formation of DSBs which then produce 1-deoxysphingolipids (1-deoxySLs)

1-deoxySLs cannot be degraded or converted into complex sphingolipids

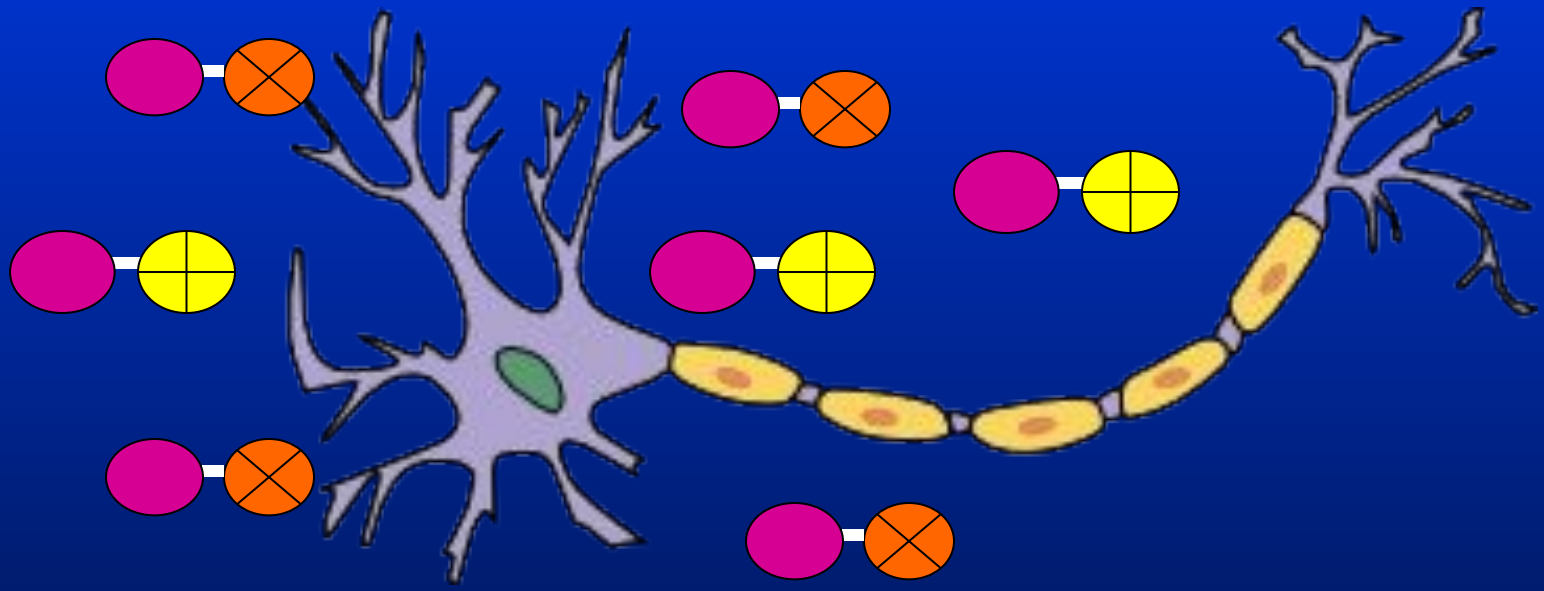


deoxymethylsphinganine
made when SPT uses glycine instead of serine

deoxysphinganine
made when SPT uses alanine instead of serine

What Happens to the 1-deoxySLs?

1-deoxySLs accumulate in the cell (specifically in the peripheral nerves) where they have been shown to have pronounced neurotoxic effects



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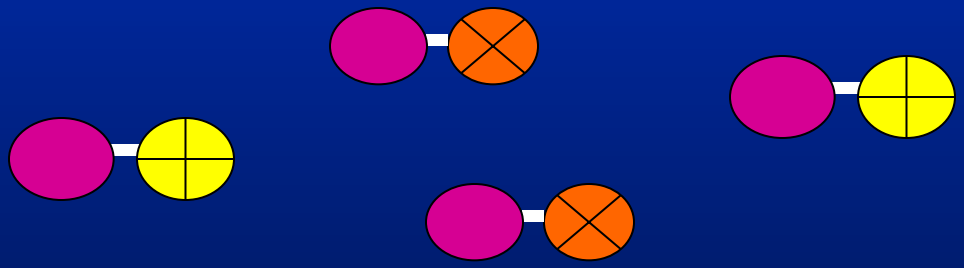
In addition to HSAN1, elevated levels of 1-deoxySLs have also been observed in patients with:

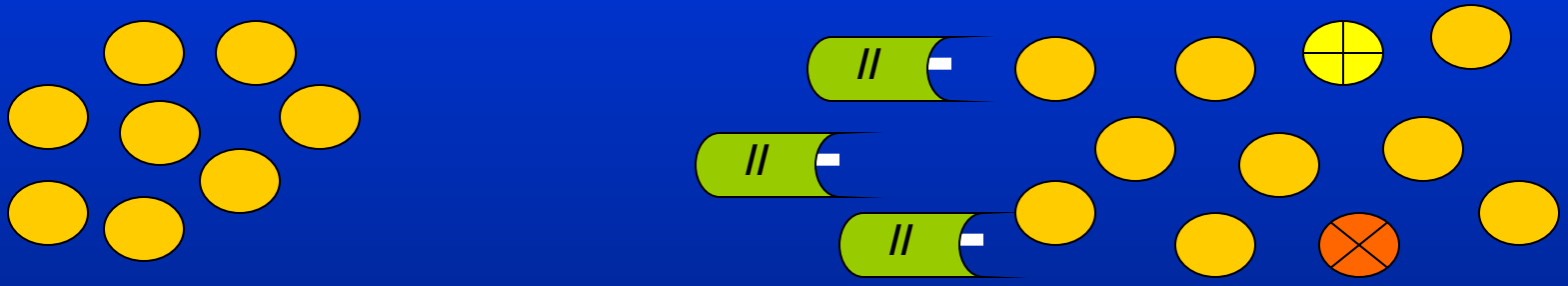
- **type 2 diabetes**
- **diabetic neuropathy**
- **chemotherapy-induced peripheral neuropathy**



What Could This Mean for HSAN1 Patients?

Treatment with L-serine supplementation

Mutated SPT has better chance of picking up L-serine instead of alternate amino acids



Prevention of the formation and accumulation of toxic 1-deoxySLs = <u>slowing or stopping of HSAN1 disease progression?</u>

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Have There Been Any Studies of L-serine Supplementation in HSAN1 Patients?

- 12-week Pilot Study (2009)
- 2-year Clinical Trial (2013-2014)

Both under the direction of:

Dr. Robert Brown, University of Massachusetts Medical Center

&

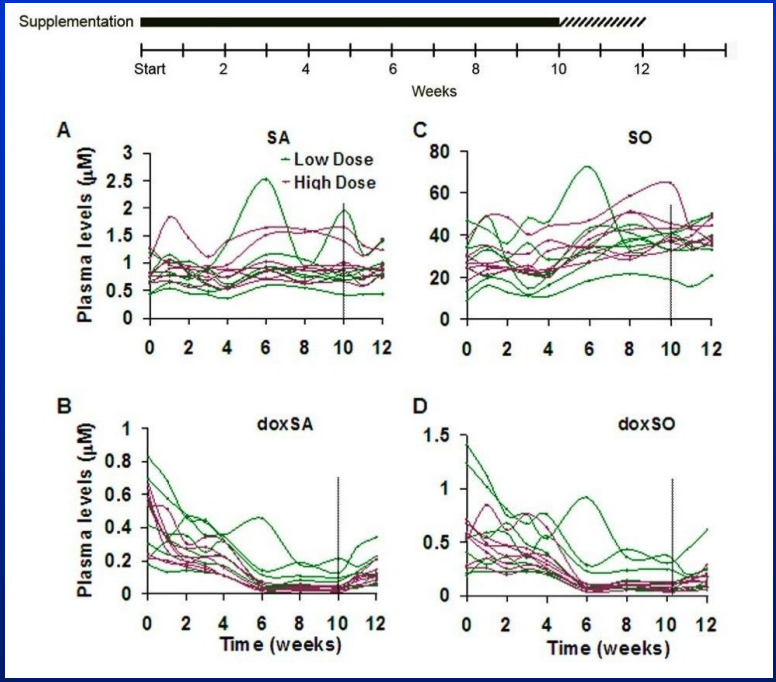
Dr. Florian Eichler, Massachusetts General Hospital

12-Week Pilot Study

14 HSAN1 patients treated with low-dose or high-dose L-serine supplementation

Results:

significant reduction in plasma 1-deoxySL levels (see graph below)
improved motor performance
increase in unmyelinated sciatic nerve fibers



eichler.mgh.harvard.edu/hsan1/

2-Year Clinical Trial

2 year randomized, placebo-controlled, double-blinded, parallel group trial

16 HSAN1 patients (ages 18-70)

Year 1: treated with placebo OR high-dose (400 mg/kg/day) L-serine supplementation

Year 2: ALL treated with high-dose (400 mg/kg/day) L-serine supplementation

Results:

- Significant reduction in plasma 1-deoxySL levels (with near-normal levels achieved within 24 weeks after L-serine treatment initiation)
- Significant quantitative improvement in motor performance, as evaluated by Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS) scale, in original L-serine treated patients
- Similar rates of CMTNS performance in crossover L-serine treated patients
- No serious adverse effects related to L-serine supplementation at 400 mg/kg/day dosage

Trial Conclusion: High-dose oral L-serine supplementation appears safe for HSAN1 patients and can potentially slow disease progression

Fridman, et al. Randomized trial of L-serine in patients with hereditary sensory and autonomic neuropathy type 1. *Neurology* 2019;92;e359-e370.

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Next Steps?

1. Creation of HSAN1 Patient Registry

Secure centralized online location for data collection, repository, and analysis

For use by HSAN1 patients and their doctors to increase standard of care

For use by researchers to advance disease understanding and potential treatments

2. Prospective L-serine supplementation study in children

Even though symptoms typically do not present until late first or second decades of life, HSAN1 neuron involvement and impairment most likely occurs in childhood, possibly even during infancy or *in utero*

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