Deater Foundation, Inc.
PO Box 255
White Deer, PA 17887
www.deaterfoundation.org / godfi.org

THE DEATER FOUNDATION, INC.
NEWSLETTER MAY 2025
ADVANCING RESEARCH TO DISCOVER TREATMENT AND A CURE FOR HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY TYPE 1 (HSAN1)

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What is HSAN1?

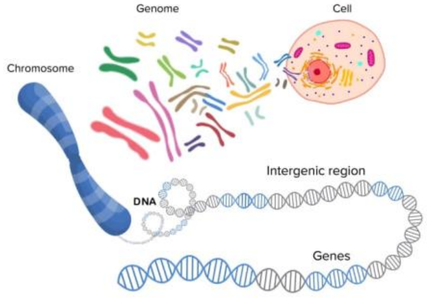
HSAN1, is a rare inherited peripheral neuropathy. Each child of an affected parent has a 50 percent chance of inheriting the affected gene. HSAN1 patients develop severe loss of sensation to temperature, pressure, and pain. This sensory loss often leads to painless injuries, chronic skin ulcers, bone destruction, bone infections, pain, amputation, and, eventually, difficulties with movement. (Neuropathy Commons)

It is caused by mutations in genes involved in sphingolipid biosynthesis, specifically the SPTLC1 and SPTLC2 genes, which encode subunits of the enzyme serine palmitoyltransferase (SPT).

What's the difference between DNA, a chromosome, a gene, and a protein?

DNA is a chemical compound that makes up everyone's genetic code. It's made up of only four chemical subunits abbreviated by the letters: A, T, C and G. These letters form together in different three letter "words" that cells can read. These words provide step-by-step instructions that tell an organism how to develop and function.

A chromosome is simply a super long piece of DNA. Humans have 23 pairs of chromosomes. One of each chromosome pair comes from mom, and the other from dad. Chromosomes are numbered 1-22 and the 23rd pair is either XX (for females) or XY (for males).



A gene is a specific stretch of DNA on a chromosome. Genes contain the exact instructions needed to make a certain product.

A protein is the product made from a gene. Each protein has a specific job in the body.

In HSAN1, there is a switch (mutation) in the DNA letters of a specific gene (SPTLC1) located on chromosome 9. This mutation causes an incorrect "word" to be formed which then makes a faulty protein. Mutations in a second gene (SPTLC2) located on a different chromosome, chromosome 14, can also cause HSAN1. SPTLC1 and SPTLC2 are small protein subunits that combine (plus a third) to form a bigger protein, called SPT.

What exactly is SPT?

Serine palmitoyltransferase (abbreviated SPT) is the protein that's affected by the HSAN1 mutation. SPT acts as an enzyme. Enzymes are proteins that help out during chemical reactions in the body. SPT helps in the very first step of the chemical reaction that makes something called a sphingolipid. In this first step, SPT takes two molecules (Palmitoyl CoA and L-Serine) and combines them into a new product.

HSAN1 mutations cause issues with how SPT functions because it alters the protein shape/structure. So instead of only grabbing the correct molecule (L-Serine) for that first step, it gets a little sloppy and can grab an incorrect one (L-Alanine or L-Glycine) as well. This mistake in the very first step causes the wrong end product to be formed.

What are sphingolipids?

Sphingolipids are primarily found in the membranes of nervous tissue. They play an important role in structure and support. They also help with cell communication and relaying messages/signals. To make sphingolipids, Palmitoyl-CoA initially combines with L-serine (with the help of SPT) to form an intermediate that is then further built upon to form ceramide.

Ceramides then can be used to form the more complex sphingolipids, like sphingomyelin and glucosylceramide.

How do you determine if you have HSAN1?

The answer is through genetic sequencing. Since many neuropathies share outward clinical similarities, the way to know for sure is by looking at the gene level. During DNA sequencing, the order of "letters" (A, G, T and C) is mapped out and any variations, or mutations, can be determined. There are many companies that offer genetic sequencing.

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Dr. Robert H. Brown, Jr., D.Phil., M.D.

Director, Neurotherapeutics
Donna and Robert J. Manning
Chair in Neurosciences
UMass Chan Medical School

This is a brief summary of the components of our study of the biology and therapy of HSAN1. For these studies we have been fortunate to have an outstanding graduate student (Sumita Nayak), a talented research technician (Erinn Ives) and an excellent post-doc (Justin Lee). As well, we have benefited as always from the expertise and guidance of Teresa Dunn at USUHS in Bethesda MD. We also stay in touch with our friend and colleague Florian Eichler. The highlights of our activity recently have included the following.

1. ***Mouse HSAN1 Model.*** We have extensively characterized the mouse model in which the Deater mutation (C133Y) is inserted into the mouse genome. These mice are an excellent mimic of the molecular pathology of HSAN1 but do not have an overt sensory neuropathy (studied in considerable behavioral detail) or motor dysfunction. We are performing electron microscopy of the sensory nerves and dorsal root ganglia to look further into the mutant vs control mice.

2. ***ASO Therapy.*** We have continued to collaborate with Jonathan Watts, PhD, here at UMass Chan Med School to develop and test panels of ASOs that suppress expression of the SPTLC1 using anti-sense oligonucleotides (ASOs). We have tested these extensively using both our mouse model of HSAN1, in which the causative mutation in the Deater family has been put into the mouse genome, and in fibroblast lines from the Deater family. We have achieved suppression of the gene in the Deater fibroblasts and in the mouse model; in our view we would prefer to have stronger potency of the ASO. Accordingly, one of our current efforts now is to make additional panels of ASO for both the mouse and the fibroblasts.

3. ***Studies of Fibroblasts, Serum and Tissues.*** As you recall, both the fibroblasts in culture and the mouse reveal elevated levels of the toxic sphingoid bases (deoxyceramide). We have established that the elevated deoxyceramides are present mainly in serum and dorsal root ganglia, to a lesser extent in sciatic nerve, and not in liver. Moreover, in our mice, levels in serum are amplified by high alanine diets as they are in people with SPTLC1 mutations.

4. ***Deater Stem Cell DRG.*** We have initiated and are studying cultures of human dorsal root ganglia from both Deater and control fibroblasts. These are obtained by generating stem cells which are then differentiated into dorsal root ganglia cultures. At least one of our ASOs shows good knockdown of the SPTLC1 gene in the Deater dorsal root ganglia cultures.

5. ***Small Molecule Therapy.*** Since the SAB meeting in fall, 2025, we have initiated a new set of experiments examining the possibility that small molecules might be effective in blocking the active site of the mutant SPTLC1. Such molecules would potentially offer advantages over the ASO therapy. The small molecules would ideally be administered in oral pills, as compared to ASOs which likely require repeated spinal taps. We have taken two approaches

    a. ***Computer Drug Screens.*** We are working with a European company to run a computer simulation of how millions of drugs might interact with SPTLC1 (as gauged by a computer program that looks at the structure of the target SPTLC1 and the drug structure, to see how they might interlock. (This is a kind of lock-and-key model). This modelling is about 1/2 completed, using the computer version of the non-mutant SPTLC1 protein. We are also doing the computer simulation with a computer-generated version of SPTLC1 that harbors the Deater mutation. Once the initial structures are available from the computer predictions, we will have many of them chemically synthesized to be tested in a real assay (5c below).

Cryo-Electron Microscopy of Deater SPTLC1. As an additional element, we are also obtaining a new analysis of the structure of the SPTLC1 protein with the Deater mutation (C133Y). We cannot be completely confident that the computer-generated version of the Deater SPTLC1 reflects the real structure. To address this, we have now engaged an electron microscopy core at UMass to determine the actual structure of the mutant protein (with the Deater variant C133Y). This method involves a process of slowing the motion of the atoms to be imaged using extreme cooling; the process is designated "cryo-electron microscopy". We hope that we will have data from this sub-project this year.

b. ***Screening all FDA-approved Drugs.*** We are also testing actual drugs in the assay below. For this real life (not computer) testing we will screen a library of nearly all of the FDA-approved drugs. The rational here is that any "hits" might be readily useful in clinical trials, since they are already FDA-approved and in use in humans.

c. ***Assaying Suppression of SPTLC1.*** For both 5a and 5b, we are using a screening assay in which we measure the enzyme activity of the SPTLC1 molecule and related proteins in the SPTLC1-SPTLC2 complex. We compare the activity at baseline and after adding the drugs, seeking those drugs that reduce the activity. We are most grateful to Paul Thompson, PhD, here at UMass Chan Med School. Paul has longstanding expertise in such large screens and has agreed that we can run this with his team in his lab.

As this suggests, we have an active program with a small but expert team onsite and amazing collaborators off site. With this team, we feel we are making meaningful progress in the drive to find therapy for HSAN1. We are keenly aware that there is much to be done but remain committed to this effort. As always, we are very grateful for the support of the Deater Foundation.

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The Cost of Research

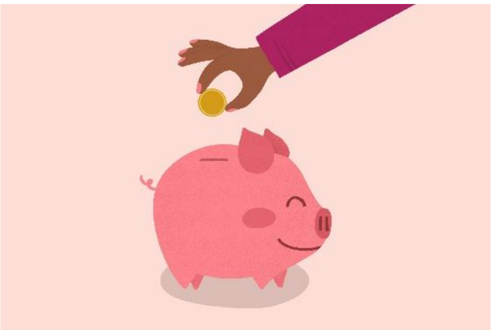
Dr. Brown is very excited about the new set of experiments described above under **Small Molecule Therapy**. This therapy has the potential to provide a faster route to a less invasive treatment for HSAN1. The Foundation believes supporting this work is an excellent use of its resources and wanted to list the estimated cost of the necessary components. We would be grateful for any support towards this new set of experiments.

Computer Drug Screens. Estimated cost of initial screen **$17,000** and **$2000** for every 10 molecules synthesized

Cryo-Electron Microscopy of Deater SPTLC1. Estimated cost **$25,000**

Screening all FDA-approved Drugs and Assaying Suppression of SPTLC1. *Estimated cost **$20,000***

Deater Foundation Inc Treasurer's Report



Balance as of 4/1/24	$20,439.82
Income:	
Contributions 4/1/24 to 12/31/24	20,435.14
Interest 4/1/24 to 12/31/24	10.17
Contributions 1/1/25 to 3/31/25	5,950.00
Interest 1/1/25 to 3/31/25	3.77
Total Income	26,399.08
Expense:	
PayPal Service Charges	- 6.95
Total Expense	6.95
Balance as of 3/31/25	**$46,831.95***

*Please note: $10,700.00 of the balance is designated for a special research project of Dr. Brown's.

Request for Giving by Eric Newcomer, President DFI

This year's newsletter includes encouraging updates on advancements in HSAN1 treatment. It's with this positive news in mind that I reach out to you with a request.

The Deater Foundation has always operated leanly, and I remain incredibly proud of our team and the significant impact your contributions have made within the HSAN1 community. Earlier this year, Dr. Brown presented three promising research opportunities that strongly aligned with the Deater Foundation's mission. We made the strategic decision to dedicate most of our resources to these initiatives, which unfortunately has left us with limited funds for any new opportunities that may arise.

While we understand that many are mindful of the current economic climate, I am respectfully asking if you would consider donating any amount. I want to assure you that the Deater Foundation board is committed to the responsible stewardship of your generosity. We are a volunteer-run organization with no paid staff or special interest affiliations. Apart from minimal platform fees, your entire donation directly supports critical HSAN1 research.

We've also learned that some companies offer donation matching programs for their employees. Additionally, we recently worked to reduce the processing fees on our online donation platform to ensure more of your contribution benefits the foundation directly.

For those who prefer to donate by mail, contributions can be sent to: The Deater Foundation, PO Box 255, White Deer, PA 17887

As a 501(c)(3) organization, all donations are tax-deductible.

Thank you for your continued support and thoughtful consideration.

Deater Foundation, Inc. Scientific Advisory Board Meeting, September 30, 2024

Researchers in attendance: Dr. Robert Brown, UMASS Chan; Dr. Florian Eichler, MassGeneral/Harvard; Teresa Dunn, USUM; Carsten Bonnemann, NIH; and Claire Le Pichon, NIH as well as Sushmita Nayak (graduate student in Dr. Brown's lab) and Erinn Ives (research associate in Dr. Brown's lab).

The meeting lasted a bit over an hour and felt like a mini symposium. The meeting consisted primarily of research from Dr. Brown's lab presented by Sushmita, along with interjections of questions and discussion throughout her presentation, followed by an ending discussion among all the researchers regarding outstanding questions and possible new insights to think about and try.

Sushmita's presentation focused on four main areas:

1. Investigating disease biology + opportunity for therapeutic interventions
2. Knock-in mouse model
3. Developing ASOs that target the human SPTLC1 gene
4. Future studies

Dr. Brown's lab has been working on many different areas of research, putting in a lot of time and effort, attacking the disease from all sides. Designing and redesigning ASOs, looking into possible new biomarkers, working on the mouse model (sensory/motor evaluation, diet manipulation, PET scan/tissue imaging, etc.), and looking into possibly designing a drug for SPT-alanine binding inhibition.

Some big questions that seemed to be present at the end of the meeting:

1. How (if possible) to produce clinical phenotype in the animal model?
2. Possibly update reagent/model? (siRNA vs ASOs, rat vs mouse)
3. What really is the role of deoxysphingolipids?

Dr. Brown's lab will consider the ideas generated as they move forward and generate more data for evaluation. There is truly an amazing team of researchers thinking about and working on this disease. With such intelligent, driven, and capable people involved our family (along with the entire HSAN1 community) is definitely in good hands.

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Deater Foundation, Inc Annual Business Meeting

The Deater Foundation, Inc. was established May 2, 1990. Currently, the Board is made up of Deater family members, including those with lived experience of HSAN1. Members live in 4 different states.

The 35th Annual DFI Business Meeting will be held remotely on Tuesday June 24, 2025 at 7pm (Eastern Daylight Time).

All are welcome to attend! If interested, please email us at deaterfoundation@yahoo.com prior to that date for the link information.

Raise the Region – Cindy Newcomer

I'm thrilled to share the exciting news of Deater Foundation Inc.'s recent participation in the Raise the Region campaign, a 30-hour online giving event that brings together community members to support local non-profits.

While this initiative is centered in central Pennsylvania, its online platform, expertly hosted by the First Community Foundation Partnership of PA, allowed us to connect with supporters worldwide. The Foundation's provision of valuable resources like advertising significantly amplified our reach, which would have been challenging for us to achieve independently due to budgetary constraints.

Thanks to the incredible generosity of twenty-three unique donors, we successfully raised $3,575 this year. This represents a commendable four percent increase over our 2024 results, and we were particularly encouraged that nearly sixty percent of our donors were new to our cause this year.

The campaign kicked off with an inspiring event that Eric and I attended. It was a fantastic opportunity to connect with representatives from other non-profit organizations and meet many enthusiastic individuals eager to learn about our missions and contribute to worthy causes.

The following morning, Eric and I, along with our daughters Alexis and Lindsey and our dear friend Bekah, had an early start in front of the WNEP – Channel 16 cameras. We had a blast showcasing our **Deater Foundation T-shirts** and **QR code posters** for the 4:30 to 6:30 am news viewers. Thankfully, the station aired clips of our enthusiasm throughout the day, ensuring our message reached a wider audience.

We are already looking forward to participating in Raise the Region again in 2026. As soon as the dates are announced, we will be sure to share all the details on our website and Facebook page so everyone can join us in supporting our mission.

Shown left to right: Alexis, Bekah, Nikki Krize (WNEP-16), Cindy, Eric, Lindsey, and Ren in front

The Deater Foundation gratefully acknowledges the generous donation given by Rory Robb in memory of her husband, Larry Deater, to fully fund the research of Drs. Brown and Thompson to screen FDA approved drugs and assay the suppression of SPTLC1 toward a treatment of HSAN1

Memories from Mona Deater Montross: Sunday School in Stull

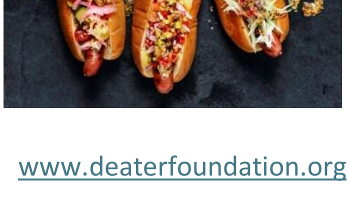
I'd like to tell you a little about the kids that came to Sunday School. I was a leader and played with all kids in the neighborhood, so when I heard Mom ring the bell and knew I had to go I would tell the others, if I have to go you have to go, so I'd take them with me to hear the word of God. One of the first ones was Pete. I remember the first day I saw Pete. It was the day they were moving in the house where the people from the Ranch had moved out. I heard the chickens squawking and looked over the bank and there was Pete catching our chickens and swinging them around by the head until the heads came off. "Hey, what do you think you are doing?" I yelled at him. He yelled back, "None of your business" I jumped down over the bank to where he was and made it my business. They were our chickens, and we needed them to live. That was our first fight. But Pete came to hear the Bible with me. He also brought his two brothers with him.

There was Eve and Porky. Eve taught me how to fight. She said we had to fight to survive and sometimes I believed that. She had always lived in a rough area and if she said fight, we fought. If she said run, we ran. The Diamond kids were four and they brought their mom with them. Then the kids from the other hill started coming. The other hill was a half mile away. That's when we became known as a Sunday School and had a regular set time, eleven o'clock in the morning. Peg, who was my age and became my best friend said, "It's not Sunday School if we don't take up a collection", and every Sunday she brought an offering, so we started gathering the offerings. Soon we were able to buy Sunday School books for all.

Connie came and brought her young brother, Jim, who wouldn't sit still unless she put him in the large rocking chair and set in front of him. One Easter, Jim ate the center of our Easter dinner pie with his hands. When Mom scolded him, he just said, "Dat was dood tho."

Then the Pattons, sometimes five and sometimes six. Often the kids from the other hill would not go home after Sunday School but stay to eat dinner and play. Mom would always make what we had go around. Many times she added water to the pot of beans, which was often our Sunday dinner, with home made bread and fresh milk.

ALL ARE WELCOME!



The Deater Family Reunion will be on Saturday, July 19 at 12 noon behind Leroy and Isabelle's house, 143 Stonetown Rd, Noxen, PA Pot Luck -everyone bring food to share. People coming from out of state please buy a bag of chips or cookies or such. Bring your own plates, utensils, drinks, and cups.

Meet Sushmita Nayak, graduate student in Dr. Brown's Lab

My name is Sushmita, and I am deeply passionate about uncovering the genetic mechanisms underlying neurodegeneration. I completed my B.S. in Biological Sciences from Amity University, India, in 2016. After graduation, I joined a diagnostic lab where I focused on identifying causative mutations for rare genetic neurological diseases within Indian patient populations. This experience exposed me to the challenges faced by the rare disease community and ignited my desire to contribute to finding therapeutic interventions for these often-overlooked conditions.

Motivated by this, I pursued a Master's in Stem Cell Biology at the University of Minnesota in 2017. My time there deepened my interest in the molecular basis of neurodegenerative diseases. After completing my Master's, I worked in the biotechnology industry, where I gained valuable experience in early-stage neurodegenerative disease biology, drug discovery, and target validation.

Building on this blend of industry and academic experience, I began my Ph.D. at the University of Massachusetts Medical School in 2022. In May 2023, I joined the Brown Lab as a Graduate Student, where I am now focused on finding therapeutic strategies for Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1). I aim to combine my industry expertise in drug development with my academic experience in disease biology to uncover novel mechanisms of HSAN1 and identify potential therapeutic targets, with the goal of advancing treatments for this rare and debilitating condition.

I live with my husband in the town of Shrewsbury. In my free time, I enjoy playing pickleball, badminton, and chess. When the weather is nice, I love going on hikes with my husband and friends. I'm passionate about traveling and discovering new cultures—learning about different ways of life fascinates me.

International Collaboration: Peripheral Nerve Society Annual Meeting

I attended the **Annual PNS 2025 Meeting**, held from **May 17th to 20th in Edinburgh**. This was my first time at the conference, hosting over 1,000 delegates, and it was truly an inspiring experience to connect with so many researchers and clinicians dedicated to the study of **peripheral neuropathies**. I participated in several insightful sessions covering a range of diseases from diabetic neuropathy and Charcot-Marie-Tooth disease to other inherited rare neuropathies, among others. The key themes that stood out to me from the conference were:

1. Advancements in diagnosis and characterization of peripheral neuropathy cases.
2. Cutting-edge techniques, including transcriptomics, for studying tissues affected by peripheral neuropathies.
3. Updates on current clinical trials and novel therapeutic approaches in CMTR, TTR amyloidosis and other peripheral neuropathies.

Beyond the sessions, I had the opportunity to engage with several researchers working on HSAN1. It was exciting to learn about their ongoing projects and explore potential future collaborations. Sharing my own research progress and developments in HSAN1 with this expert community was a valuable experience. I'm especially grateful to the Deater Foundation for providing me the opportunity to be part of such an enriching event. Their support enabled me to connect with a global network of experts—all in one place

T-shirt fundraiser – Alexis & Lindsey Newcomer

We are excited to announce that Deater Foundation T-shirts featuring our latest logo and a QR code are now available for purchase! These shirts were initially created for Raise the Region 2024 to help us stand out and show our unity during the WNEP – Channel 16 early morning broadcasts.

Due to positive feedback, we have continued to produce these shirts and even made transfers, and a heat press available at last year's reunion for family members to create their own. We will keep making shirts to support the Deater Foundation.

An order form will be available on our website by the time you receive this newsletter. Each shirt comes in a variety of colors and includes a QR code on the sleeve that directs people to the foundation's website. When ordering, you can specify the placement and size (large or small) of an additional logo.

To place an order, please visit our website at www.deaterfoundation.org or www.godfi.org to access the order form. Once completed, you can email it to ericnwcmr@gmail.com or mail it to Eric Newcomer, 5479 Clarkstown Rd., Muncy, PA 17756. This information will also be included on the order form for your convenience.

Thank you for your ongoing support of the Deater Foundation.

Deater Foundation, Inc.
PO Box 255
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