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

The Deater Foundation, Inc.
Newsletter May 2023
Advancing research to discover treatment and a cure for Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1)

Journal of the American Medical Association, June 3, 1939: Vol. 112 No. 22

An arresting example of the influence of heredity in disease is the development of the same chronic pathologic process in two or more members of a family when they reach a specified age. The family in the two cases herein reported furnishes such an example. In October 1937 Dr. J. Torrance Rugh of the department of orthopedics received a letter from two young men claiming they "were very interesting cases" and would like to be studied and treated at this hospital. Trophic and vasomotor disturbances with dissociated sensory changes, usually of the lower and sometimes of the upper extremities, were found in most of the male and in a few of the female members of a family some of the member of which also had harelip and cleft palate. .. The syndrome seems best attributed to an organized dysgenesis of the central nervous system of the type described by (Alfred) Fuchs under the term myelodysplasia.

Perforating Ulcers of Feet, With Osseous Atrophy in a Family with Other Evidences of Dysgenesis L.M. Tocantins, M.D. and H.A. Reimann, M.D.

Also noted in the 1939 article: "the father of our two patients ..has also had ulcers in several fingers from which spicules of bone would extrude spontaneously or he would extract them himself with pliers. At the present time he has no index or little finger on the right hand.
This phenomenon continues in current generations. Asked, "How often do you come across painless bone extrusions as part of other hereditary neuropathies?" Dr. Florian Eichler, "I have only seen it in the Deater family." And Dr. Reza Seyedsadjadi, "Not very commonly but described in HSAN. I cannot think of any other CMT type with bone extrusions to this extent." Private communication 2022

Muscle Nerve. 2015 Apr; 51(4): 489–495.
Published online 2015 Feb 11. doi: 10.1002/mus.24336

Hereditary sensory and autonomic neuropathy type 1 (HSAN1) is most commonly caused by missense mutations in *SPTLC1*.
Small-fiber polyneuropathy (SFPN) is prominent in hereditary sensory and autonomic neuropathy type 1 (HSAN1) and contributes to many symptoms, including sensory loss, neuropathic pain, and tissue necrosis.
The first symptoms were universally sensory and occurred at a median age of 20 years (range 14–54 years). The onset of weakness, ulcers, pain, and balance problems followed sequentially. Skin biopsies revealed universally absent epidermal innervation at the distal leg with relative preservation in the thigh.
Twenty-three patients with HSAN1 (10 men, 13 women) completed the HSAN1 survey. Twenty were from an extended family with the C133Y mutation in *SPTLC1*, and 3 were from a family with the C133W mutation.

Natural history and biomarkers in hereditary sensory neuropathy type 1

Vera Fridman,[1] et. al.

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The excerpts above from publications 76 years apart illustrate the gains in knowledge about HSAN1 due in part to the dedication of Deater family members in subjecting themselves to repeated testing and inquiry over the years. Following the initial study initiated by Harvey and Russell Deater, multiple family members participated in other studies in the intervening years at the National Institutes of Health and Massachusetts General Hospital and most recently with research into associated macular telangiectasia. Genetic exploration has also found a mutation in the same pathway connected to childhood onset Amyotrophic Lateral Sclerosis (ALS). In 1990 the family established the Deater Foundation, Inc. to further fund HSAN1 research.

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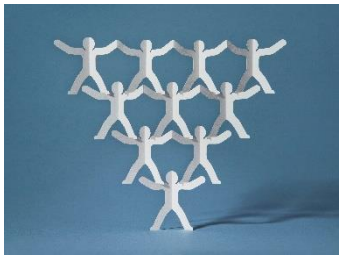
Hereditary Sensory and Autonomic Neuropathy Symposium – Finally!



In 2022 the Deater Foundation, Inc. sponsored a virtual symposium, originally scheduled to be held in person, in 2019. The covid pandemic intervened. Researchers from around the world participated as did some interested lay people. Dr. Robert H. Brown, Jr., University of Massachusetts Chan Medical School and Dr. Florian Eichler, Massachusetts General Hospital and Harvard, were co-chairs of the meeting.

Friday, September 9, 2022, 10 a.m. to 5:30 p.m.	
10:00 a.m.	**Dr. Robert H. Brown, Jr., D.Phil, M.D., and Florian Eichler, M.D. and Deater Family** *Welcome & Introductory Comments*
I. HSAN1 - Clinical and Molecular Update	
10:15 a.m.	**Florian Eichler, M.D. Mass General Hospital/Harvard** *Clinical Spectrum of SPTSSA Related Disease: from Mice to Human* Focused on the expanding spectrum of SPT-related diseases and recent research happening in sphingolipid biology. Specifically, the role of ORMDL proteins and the regulation of cellular sphingolipids via the small subunits of SPT. While not directly about HSAN1, this could help widen the field in terms of better understanding sphingolipid biology, potentially leading to new ways of thinking about neurodegeneration and therapeutic strategies.
11:00 a.m.	**Ingo Kurth, M.D. Aachen University Germany** *Overview: Genetics of Inherited Hereditary Sensory and Autonomic Neuropathy* Summary of monogenic neurodegenerative disorders involving altered pain perception (loss or gain), of which HSAN1 is included. Many of these disorders may share commonalities in mechanism, and understanding these in a larger sense could ultimately be beneficial for the treatment of HSAN1.
II. Update - HSAN1 Models	
1:00 p.m.	**Hongjie Zhang, Ph.D. University of Macau** *A Model of HSAN1 Reveals a Role of Glycosphingolipids in Neuronal Polarity* Presented work involving *C. elegans* (worms) model of HSAN1 finding that, in this organism, SPTLC1 mutation confers a loss of function effect, possible vesicular trafficking involvement, and effect on glucosylceramide levels.
1:30 p.m.	**Theresa Dunn, Ph.D. Uniformed Services University** *Pathogenic Mutations in SPT Cause Multiple Neurodegenerative Diseases* Overview of mammalian cell based research focusing on new insights into ORM regulation of SPT and possible therapeutic implications. SPT consists of SPTLC1/SPTLC2/SPTSSA/ORMDL3 complex. Mutations can affect different aspects of SPT, such as substrate selection, ceramide sensing, and ORM regulation.
2:00 p.m.	**Robert Burgess, Ph.D. The Jackson Laboratories** *Modeling: HSAN1/SPTLC1 in Mice* Discussion focused around making precise (face, construct and/or predictive validity) models of inherited peripheral neuropathies (demyelination, axonal, and HSAN1) in mice. Important work to ensure the model/mechanism is correct, and the observed phenotype is arising for the right reasons which could then translate over into human cells and patients.
III. SPTLC1 Motor Neuropathy	
3:00 p.m.	**Payam Mohassel, M.D./Carsten Bonnemann, M.D. National Institute of Neurological Disorders and Stroke** *Excess Sphingolipid Synthesis and Motor Neuron Disease* Discussion on the neurodegenerative disease, juvenile amyotrophic lateral sclerosis (jALS), which involves a progressive degeneration of the upper and lower motor neurons. Different variants in the same gene may manifest with different phenotypes which can be challenging in terms of classification. Different mutations in exon 2 of SPTLC1 (same gene as HSAN1) have been shown to cause various forms of early onset ALS that differ from HSAN1 both

	biochemically (excess sphingolipid biosynthesis instead of deoxysphingolipids) and in terms of regulation. Also discussion on mixed phenotype: S331 syndrome, which is a severe and atypical form of HSAN1 that presents with elevated levels of both types of sphingolipids mentioned above.
3:30 p.m.	**Claire Le Pichon, Ph.D. National Institute of Child Health and Human Development** *Precision Mouse Models of Childhood ALS Caused By Excessive Sphingolipid Synthesis* Research on using mouse models of disease to study genetically caused neurological syndromes as well as pathology arising from traumatic nerve/brain injury and subsequent cell type specific responses to these injuries. Specifically how mutations lead to dysfunction and degeneration and affect some cell types more than others. Mutations in exon 2 of SPLTC1 linked to jALS cause a lack of negative regulation of SPT pathway. When looking at that hypothesis in mice, elevated sphingolipid levels and evidence of neurodegeneration were observed.
IV. Deoxysphingoid bases in HSAN1, diabetic neuropathy and beyond	
4:30 p.m.	**Thorsten Hornemann, Doctor rer. nat. University of Zurich** *Sphingolipids and Neuropathies* Sphingolipids are very complex, with numerous and specific functions. Deoxysphingolipids affect axons by causing a decrease in neurite outgrowth, not the cell body, initially. ALS mutants show an altered ER localization, reduced ORMDL3 interaction, and disruption of sphingolipid homeostasis. Diabetic neuropathy is similar to HSAN1, and deoxysphingolipid levels are also elevated. In diabetes, there is a disturbance in the serine to alanine ratio which drives formation of dSLs.
Saturday, September 10, 2022, 10 a.m. to 1:00 p.m	
V. HSAN1 Therapies	
10:00 a.m.	**Florian Eichler, M.D./Vera Fridman, M.D. Mass General Hospital/ Harvard; University of Colorado** *Small Molecules and Other Approaches* Discussion on treatment and challenges in CMT with disease modifying therapies: different approaches using miRNA in AAV9 vector and lumbar intrathecal injections.
11:00 a.m.	**Huiya Yang, Ph.D. UMass Chan Medical School (former)** *Biologic Therapies* Targeted therapy to inhibit production of deoxysphingolipids while maintaining normal function of SPTLC1. One possible treatment is to use antisense oligonucleotides (ASOs) therapy to suppress mutant SPLTC1. First steps would be pre-clinical: *in vitro* and *in vivo*. Multiple ASOs that target different areas of human SPTLC1 have been designed. C133Y knock-in mouse model has been generated but still in active breeding stage. These mice can hopefully then provide a model for testing therapeutic interventions.
11:30 a.m.	**Vincent Timmerman, Ph.D. University of Antwerp** *Neuropathy Screening – NP4 Video* Presented work on a phenotyping platform for screening therapies in peripheral neuropathies. This screening system would have the potential to accelerate testing of different drug compounds and also eliminate the need to create models for each mutant in question.
12:00 p.m.	**ALL** *General Discussion moderated by Dr. Robert H. Brown, Jr.*

UMASS Chan Medical School

Robert H. Brown Jr., DPhil, MD, the *Leo P. and Theresa M. LaChance Chair in Medical Research* UMass Chan Medical School

I am pleased to report that over the last year we have confirmed that we have a new mouse model of HSAN1. In this mouse line, generated by Dr. Huiya Yang jointly with the company Biocytogen, the Deater family mutation in SPTLC1 (Cysteine 133 Tyrosine, also labeled C133Y) is "knocked into" the mouse gene. This is similar to the work previously accomplished by Dr. Robert Burgess for the SPTLC1 Cysteine 133 Tryptophan mutation. The C133Y mice thus far, after aging several months, have not developed neuropathy, on a standard diet. However, they do demonstrate robust production of the toxic deoxysphingolipids that are a biomarker for the HSAN1 neuropathy.

In this regard, we have been very fortunate to collaborate with Dr. Teresa Dunn, whose expertise has helped in characterizing our mice. As previously reported, Dr. Huiya Yang who helped generate these knock-in mice, and Dr. Jonathan Watts in the RNA Therapy Institute at UMass Chen Medical School have generated anti-sense oligonucleotides that inactivate the HSAN1 gene and thereby suppress the toxic lipid species. Antisense oligonucleotides (ASOs) bind to the target RNA and moderate protein expression through several different mechanisms. The ASO field is an emerging area of drug development that targets the disease source at the RNA level and offers a promising alternative to therapies targeting downstream processes. This therapy is currently being used to treat some rare hereditary diseases including Huntington's disease and Amyotrophic Lateral Sclerosis.

For these reasons, we are delighted that our HSAN1 ASOs are very effective in cells in culture. Importantly, they suppress activity of the SPTLC1 gene and the toxic deoxysphingolipids in fibroblasts obtained from Mr. Larry Deater. Our intention now is to test the efficacy of these reagents in the new mice. To facilitate these studies, we are recruiting a new research associate and a graduate student. We have been honored to receive funding from the Deater Foundation and look forward to remaining in close contact with the Foundation in the coming year.

Further, we will convene the Deater Foundation, Inc. Medical and Scientific Advisory Board this spring. We are grateful for the participation of outstanding researchers Carsten Bonnemann, M.D. (National Institute of Neurological Disorders and Stroke), Teresa Dunn, PhD (Uniformed Services University) and Florian Eichler, M.D. (Massachusetts General Hospital/ Harvard Medical School) who serve on this Board.

The Mass General Center for Rare Neurological Diseases

On March 10, 2023, Dr. Florian Eichler, Director of the Center for Rare Neurological Diseases, convened a retreat for his staff at the Royal Sonesta Hotel. The Riverfront Room had a beautiful view of the Charles River on a gorgeous, sunny day and the food was delicious. There were about 40 people in attendance. The Deater Foundation, Inc. provided the venue, having decided to hold the HSAN1 conference virtually.

"The mission of the CRND is to create new opportunities to improve the lives of those affected by rare monogenic neurological disorders by building new alliances based on insights from biology, clinical unmet needs, and recent advances in technology. Throughout strategic decision making, the patient perspective guides our process."
Dr. Eichler reports, "Your support went a long way in galvanizing our group in the Center for Rare Neurological Diseases, and we will from now on have retreats at the Sonesta every 6 months. We had a session dedicated to inherited neuropathies, and Dr. Sadjadi's coordinator presented on several ongoing studies and trials. As you know, we have also made progress on a new disease due to mutations in the small subunit of SPT. We are preparing for new trials here and expect this to shed light on some of the disparities in phenotype (HSAN versus ALS) that are currently plaguing the field, including when to give L-serine and when not. Overall hope to advance a registry for SPT related mutations in collaboration with Dr. Bob Brown. Glad to collaborate in the future and think about new trials for HSAN1."

Uniformed Services University of the Health Sciences
Support for the acquisition of a Mass Spectrometer at the Dunn Lab

Dr. Teresa Dunn, Professor and Chair, Department of Biochemistry and Molecular Biology, Uniformed Services University of the Health Sciences requested, with the support of Dr. Robert Brown, funding in the amount of $25,000.00 to relocate a Mass Spectrometer donated from another department at her institution.

The Dunn lab has a longstanding interest in sphingolipids and has worked on many projects impacting HSAN1. The Deater Foundation, Inc. has reserved the entirety of the funds for this project. Once in place, she will be working with Dr. Brown to analyze deoxysphingolipids in HSAN1 mice being treated with therapeutics designed to inhibit SPT containing the mutant SPTLC1 subunit found in HSAN1. Having the equipment will expedite the collaborative work with Dr. Brown's lab. Currently, samples from Dr. Brown's lab are put in a queue and processed when the Dunn lab has access to the instrument, about 3-5 days a month, often on weekends and holidays. Dr. Dunn says this "speaks to the dedication of my long term senior research associate, Ken Gable, who does the analysis."

The percentage of usage time on the Mass Spectrometer will depend on the amount of samples to be analyzed, but Dr. Dunn expects that as the study progresses it could easily approach 25%.

Dr. Dunn is also collaborating with Dr. Hugo Bellen, a Professor at Baylor College of Medicine in the Departments of Molecular and Human Genetics and Neuroscience. Utilizing Baylor's library of DNA bar-coded compounds, purified SPT/ORMDL complexes from Dr. Dunn's lab are incubated with the library. Compounds that are bound can be identified by their bar-codes. The compounds will then be tested for effects on SPT activity and ORMDL regulation. The efficacy of known inhibitors of SPT will be compared to see if any inhibit SPT containing the HSAN1 variants in either of the SPT subunits. HSAN1 is caused by mutations in the SPT enzyme. The ORMDLs are negative regulators of STP (serine palmitoyltransferase), the first step in sphingolipid biosynthesis.

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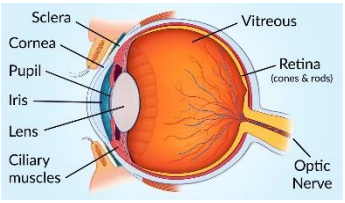
THE LOWY MEDICAL RESEACH INSTITUTE on MacTel



Committed to understanding the causes of Macular telangiectasia Type 2 (MacTel) and translating these discoveries to novel treatments.

A new treatment for MacTel, a rare, slowly progressive degenerative disease of the macula that results in gradual deterioration of central vision and is associated with HSAN1, is awaiting FDA approval. Neurotech Pharmaceuticals, Inc.'s encapsulated cell therapy is designed to be implanted into the vitreous cavity of the eye. The investigational implant is a tiny hollow cylindrical membrane which encapsulates human epithelial cells genetically engineered to produce ciliary neurotropic factor (CNTF) continuously, a protein now clinically validated in clinical trials to slow the progression of MacTel.

The Institute is nearly done with a study looking at MacTel and HSAN1: Corneal nerve fiber abnormalities in patients with macular telangiectasia type 1 (MacTel) and hereditary sensory and autonomic neuropathy type 1 (HSAN1). The aim of this study is to better understand the relationship between MacTel and peripheral neuropathies. Specifically, if patients with MacTel and/or HSAN1 show changes of their corneal nerves. The Institute hopes to enroll 4 HSAN1 participants before the summer.
Results could take approximately one year from completion of enrollment. The MacTel Registry is still enrolling participants. https://www.lmri.net/research-2/clinical-research/how-to-participate/

The Lowy Institute, along with sites in Texas, Ohio, Michigan, and Wisconsin, has started enrollment in the Phase 2a Study of the Effect of Serine Supplementation and Fenofibrate Treatment on Serum Deoxysphinganine Levels in Patients with Macular Telangiectasia (MacTel) Type 2 (SAFE Study)
This study investigates the effects of serine and fenofibrate on the levels of deoxysphingolipids in the blood of people affected with MacTel Type 2. Deoxysphingolipids are fats that have been shown to be toxic to neurons (nerve cells) some of which are found in the back of the eye. They are also linked to the development of neuropathies. These lipids are elevated in MacTel patients and perhaps treating with serine and/or fenofibrate will reduce these levels. For more information: https://clinicaltrials.gov/ct2/show/NCT04907084

The Lowy Medical Research Institute "*really* appreciates the continued support from the entire Deater family!"

Deater Foundation Inc Treasurer's Report

Balance as of 4/1/22	$49,560.13
Income:	
Contributions 4/1/22 to 12/31/22	10,749.43
Interest 4/1/22 to 12/31/22	3.47
Contributions 1/1/23 to 3/31/23	4,158.98
Interest 1/1/23 to 3/31/23	4.28
Total Income	14,916.16

Expense:	
Website Maintenance 6/21/22	400.00
Website Maintenance 9/21/22	400.00
Website Maintenance 12/26/22	400.00
Website Maintenance 3/22/23	400.00
Total Expense	1,600.00

Balance as of 3/31/23 $62,876.29

As noted in the article on Teresa Dunn's research, $25,000.00 of the current balance is allocated to relocate a Mass Spectrometer to Dr. Services Dunn's lab, donated from another department at the Uniformed University.

Amazon Smile Program Discontinued

Amazon has ended the Amazon Smile program which provided a small stipend to non-profit organizations when customers designated a preferred charity and purchased products through the Amazon website. In a message to customers Amazon said:

> *"In 2013, we launched AmazonSmile to make it easier for customers to support their favorite charities. However, after almost a decade, the program has not grown to create the impact that we had originally hoped. With so many eligible organizations—more than 1 million globally—our ability to have an impact was often spread too thin."*

The Deater Foundation is grateful to Amazon for the years of donations, and especially to our supporters who have consistently remembered DFI in this way. We are sorry to lose this revenue stream and are hopeful for your continued support through your direct donations to DFI by mail or through the website. Our small organization has facilitated big strides in research through our modest but targeted donations over the years.

With promising new research on the horizon on various fronts, we are looking forward to supporting research efforts where we can make the biggest difference.

HSAN1 Registry

by Jon Ellsworth

Last year, DFI introduced the HSAN1 Registry, which is a collaboration between the Deater Foundation and the University of Massachusetts Chan Medical School (UMass Chan).

Over the years, members of the Deater family have been involved in various research initiatives. Word of mouth has historically been the means for participation in these efforts. As the family has continued to grow, and new generations have been impacted by HSAN1, the need for a more structured database has been realized. Research has also introduced a connection with people outside of the Deater family who are affected by this disease. Through DFI's collaboration with UMass, the registry has been taking shape.

As someone who is directly impacted by HSAN1, both me and my kids, I see the registry as a vital tool in research opportunities into the future. Having contact information that is provided voluntarily allows researchers a quick connection to the right people. HSAN1 is rare, and the Deater family and DFI, along with Dr. Brown, have championed the cause and pushed research forward over the past 45+ years. Keeping researchers around the globe involved and interested in this disease is very important. The registry is another way we are able to ease the burden when they are ready to seek information or even look for participants in future trials.

If you or someone you know has HSAN1, I'd encourage you to register today! The information is securely held on UMass servers.

For more information and to register, visit DFI's website at www.godfi.org

In Memory of Carol Ann Adams Dorward

By Eric Newcomer

On Thursday December 8, 2022 we lost a very important member of the Deater Foundation.

Carol Ann Dorward was one of the visionaries that cofounded our organization and served as the president from 1990 until 2013. She was a dedicated advocate for finding a treatment and cure for HSAN1 after watching her mother and numerous other members of the family deteriorate from one family reunion to the next. She was there in the background doing all she could to help. As most of you know HSAN1 is a rare hereditary Neuropathy, but back in 1990 it was known as the Deater disease, named after Carol's maternal grandfather's side of the family and was barely talked about much outside of Noxen Pennsylvania. I encourage you to look up Noxen sometime when you'd like to see where the middle of nowhere is. I can tell you that I am honored to be only the second president of Deater Foundation and look at our global reach now! Aunt Carol recognized my interest in the foundation a number of years back and I followed her leadership as vice president until a health issue forced her to retire from Deater Foundation early in 2013. It is on her solid foundation that I can so proudly continue the work that she helped lay, now over 30 years ago.

I'd like to say Thank You Aunt Carol! for your leadership, heart, and vision, and for always being a great aunt! Love ya and I promise I'll do my very best to keep the Deater Foundation moving strongly forward.

Per her obituary: Contributions in her name may be made to the Deater Foundation, Inc., PO Box 255, White Deer, PA 17887

DEATER
FOUNDATION, INC.

DEATER FOUNDATION INC.
ANNUAL MEETING

JULY 11, 2023
7:30 PM EDT

The Meeting will be held virtually only.
To join please request access at ericnwcmr@gmail.com

Deater Family Reunion circa 1943

The **Deater Family Reunion** will be held on Saturday, July 15 at 12 noon behind Leroy and Isabelle's house, 143 Stonetown Rd, Noxen, PA

Pot Luck -everyone bring food for their family plus some extra. It all gets put out on the food table for everyone 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

All are welcome!

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