Deater Foundation, Inc.
PO Box 255
White Deer, PA 17887

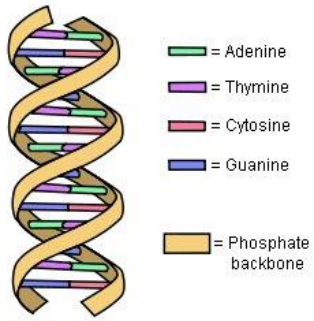
Newsletter 2020

The purpose of the Deater Foundation is to provide funding for medical research for the disease Hereditary Sensory and Autonomic Neuropathy Type1 (HSAN1) to discover a treatment or cure.

HSAN1 is an inherited genetic disorder of sensory loss beginning in the hands and feet and leading to ulcers of the skin often resulting in severe infection, muscle weakness, and bone loss. It is often characterized by severe lancinating pain and progresses from distal to proximal nerves. The disease was once thought to be of adult onset but is now recognized to be present at a young age. The research that is being supported by the Deater Foundation is centered on the mutation in the SPTLC1 gene. The SPTLC1 gene provides instructions for making one part (subunit) of an enzyme, serine palmitoyltransferase (SPT). The SPT enzyme is involved in making certain fats called sphingolipids. Sphingolipids are important components of cell membranes that play a role in many cell functions. Members of the Deater family have been involved with research into HSAN1 for more than 70 years.

Genomics Review

In nearly every cell of every living organism there exists a complete set of instructions for creating that organism and regulating its cellular structures and activities over its lifetime. That set of instructions is called a genome.



A genome is organized into distinct units called chromosomes. Chromosomes are coiled threads of deoxyribonucleic acid (DNA). DNA is composed of two long chains of nucleotides bound together in pairs to form a double helix. Sugar and phosphate form the “backbone” of the DNA. There are four different kinds of nucleotides that form the bases that lie between. Three and a half billion of these nucleotide pairs make up the human genome.

Specific sequences of nucleotide bases within a DNA strand (genes) are the cell’s instructions for producing proteins. Proteins perform a wide variety of physiological tasks. Each individual’s unique characteristics result from slight variations, called polymorphisms, in the sequence of nucleotides that comprise the genes of that individual. Other types of variations, mutations, also occur. Both polymorphic and mutagenic variations may be harmful by inhibiting the production, or altering the normal function, of a protein. At least nine mutations in the SPTLC1 gene have been found to cause HSAN1. The mutation changes protein building blocks in the SPTLC1 subunit which results in an SPT enzyme with altered activity. This altered enzyme makes molecules called deoxyspingoid bases, which it does not normally produce, and which are toxic to nerves, causing the disease.

Dr. Robert H. Brown, Jr., University of Massachusetts Medical
Ongoing HSAN1 Therapy Research

Recent work in the Brown Lab has focused on two aspects of HSAN1. One addresses therapy directly, the other indirectly through production of new mouse models. The first line of work, done by an outstanding graduate student, Huiya Yang, has been to suppress expression of one of the key mutant genes that causes HSAN1 – the long chain sub-unit of the serine palmitoyl transferase enzyme (SPTLC1). The underlying concept is that the mutant protein exerts a toxic effect on neurons by forming of a set of toxins, deoxysphingoid bases (DSBs). We believe that reducing the level of the mutant SPTLC1 gene will reduce levels of DSBs and slow or stop the neuropathy. We are exploring two approaches to gene silencing of DSBs. One project targets RNA using a class of compounds known as microRNA. This work has been co-mentored by an outstanding senior faculty member, Dr. Guangping Gao, who directs the Gene Therapy Center at UMass Medical School. Another targets RNA using anti-sense oligonucleotides (ASO); the ASO project has benefitted enormously from collaboration with Dr. Jonathan Watts, a faculty member in the RNA biology unit at UMass Medical. Dr. Yang has focused recently on the microRNA approach. For this, she has generated 24 different microRNAs that target different regions of RNA made from the SPTLC1 gene. She has screened these extensively in a cell line (HEK293T cells). We were pleased to find that many of the 24 candidate microRNAs suppress SPTLC1; four in particular are being advanced for further study. In the HEK293T cells, these four microRNAs suppress not only the SPTLC1 RNA but also the SPTLC1 protein.

One possible risk of this gene suppression therapy is that it may exceed too well. That is, if the chosen microRNA suppresses not only the diseased SPTLC1 gene but also the normal SPTLC1 gene there could in theory be adverse consequences from too little remaining SPTLC1 in cells. We have therefore taken an additional step, in which we silence the innate SPTLC1 gene but simultaneously replace it with an external version of the SPTLC1 gene that is modified so it cannot be attacked by the microRNA. This has required developing the modified SPTLC1 gene that resists the microRNAs. Huiya now has completed initial experiments modifying the SPTLC1 gene and created vectors that contain both the microRNA to turn off the innate SPTLC1 and also the external SPTLC1 gene that resists the microRNA. In pilot cell culture studies, this dual system appears to work well.

As an indirect approach for therapy development, we have undertaken experiments with our mouse core to generate new mouse models of HSAN1. In these new models, our goal is to put the HSAN1-causing mutations into the mouse genes. This differs from the previous models we have published in which we leave the mouse SPTLC1 genes intact but add external, so-called transgenes that have mutant SPTLC1. We are cautiously hopeful that we have at least one new line of mice with a knocked-in HSAN1 mutation. We will continue to work on a set of several mutations over the next months and look forward to a full report on these mice in the near term.

On behalf of all of us in the laboratory, I want to express once again our profound gratitude to the Deater Foundation for its ongoing support. We look forward to continued progress.

ENTERPRISE HOLDINGS FOUNDATION

The Deater Foundation would like to express grateful acknowledgement of the donations made by the Enterprise Holdings Foundation over the years to the Deater Foundation, Inc. As an employee of Enterprise Holdings which, through its integrated global network of independent regional subsidiaries and franchises, operates the Enterprise Rent-A-Car, National Car Rental, and Alamo Rent A Car brands, Jon Ellsworth was able to request donations through his Human Resources Department. The donations made by the philanthropic arm of the company constituted a major support for the Deater Foundation. In Jon's last year with the company we received a $1,000.00 contribution. This resource is no longer available, but Jon urges others to investigate through their manager or HR department if their company has a foundation.

Deater Foundation Inc Treasurer's Report

Balance as of 4/1/19	$46,641.17
Income:	
Contributions 4/1/19 to 12/31/19	8,747.87
Interest 4/1/19 to 12/31/19	2.71
Contributions 1/1/20 to 3/31/20	2,181.99
Interest 1/1/20 to 3/31/20	.29
Total Income	10,932.86
Expense:	
Deater Fund at UMass (August)	- 20,000.00
Royal Sonesta – Symposium deposit	- 5,000.00
Deater Fund at UMass- (January for symposium)	- 20,000.00
PayPal Service Charges	- 6.23
Total Expense	45,006.23
Balance as of 3/31/19	$12,567.80

$40,000.00 *was dedicated this year to support an international symposium on HSAN1 and related pathologies, including reserving the venue, technology support, and meals and rooms for presenters at a hotel and conference center in Boston. Because of the pandemic, the symposium has been postponed and rescheduled for March 2021. We thank the Royal Sonesta Boston for making this accommodation. We encourage your donations so we can continue to foster such research collaboration.*

The Deater Family Reunion

Is scheduled for Saturday, July 18, 2020 but plans are uncertain at this time. Please check the Deater Foundation Facebook page for updated information.

Patient-derived stem cells to characterize rare genetic disease

Jonas van lent, MSc, PhD student/ Supervisor Prof. Dr. Vincent Timmerman, PhD
Peripheral Neuropathy Research Group, University of Antwerp, Belgium

Our lab at the University of Antwerp, Belgium, has a longstanding research interest in the molecular genetics of inherited peripheral neuropathies. Specifically, we aim to gain molecular insights in underlying disease mechanisms of the peripheral nerve. One of our focus is the study of rare genetic mutations causing hereditary sensory and autonomic neuropathy type 1 (HSAN-I).

Ten years ago we discovered HSAN-I associated mutations in the SPTLC2 gene coding for one of the different subunits of the serine palmitoyltransferase (SPT). Note that HSAN-I disease causing mutations were found before in the SPTLC1 gene. From then on, we gained an increasing knowledge in the disease mechanisms of SPTLC1 and SPTLC2 mutations. In HSAN-I, the substrate specificity of the SPT enzyme is altered by mutations in one of both genes. Instead of using the amino acid L-serine, the mutant SPT enzyme now metabolizes L-alanine or L-glycine, causing the formation of neurotoxic products (known as deoxysphingolipids).

Recent clinical studies revealed that L-serine supplementation (providing an excess of L-serine will thereby decrease the relative abundance of L-alanine/L-glycine) improved the neuropathy symptoms of patients due to a reduction of the neurotoxic products. Interestingly, in collaboration with Dr. Guoliang Cui (German Cancer Research Center) we revealed a potential HSAN-I associated immunodeficiency in addition to the neuropathy. Taken together, this finding triggers us to investigate and obtain further molecular insights.

In a new project, we collect blood samples from multiple patients carrying SPTLC1 and SPTLC2 mutations. The blood is used to make induced pluripotent stem cells (iPSCs), which means the "reprogramming" of white blood cells towards a stage they can potentially form any other cell type (besides the placenta or umbilical cord).

We will grow these patient-derived stem cells and develop sensory neurons (these are neurons affected in HSAN-I) by adding small molecules in order to mimic the situation in the human body. Afterwards, we characterize these sensory neurons using advanced microscopy tools and biochemical techniques and compare the findings with neurons derived from iPSCs of healthy control individuals. The formation of neurotoxic lipids will be investigated in collaboration with Dr. Thorsten Hornemann (University Hospital Zurich, Switzerland).

The characterization of these iPSC neurons could result in new insights and explain commonalities between different SPTLC1 and SPTLC2 mutations in the HSAN-I disease mechanisms. Furthermore, our project will allow us to assess the potency of L-serine supplementation in an iPSC sensory neuron culture system and provide a platform for assessing the potential of novel disease-relevant therapeutic targets for HSAN-I.

Helping Hands by Eric Newcomer, Deater Foundation Inc. President

One of the aspects of the Deater Foundation that I am the proudest of is that we provide a platform where everyone can relate to HSAN1. Whether it be researchers, students, donors, family, affected and non-affected, involved or just interested, our website is a place where we all can share success, break-through's, difficulties, ideas and even find information to share with our own doctor's. For those who might not know, this disease affects its' victims in their own way, for some it is their feet and legs, others their hands, still others their eyes, but each person has to deal with the symptoms in their own way.

Surgical Option for Finger Contractures

In the 2019 DFI newsletter there was an article about how Paul Clemow was happy to report that an "FDS to FDP" transfer was helping him regain flexibility in his fingers. I printed a few copies of that article and took off to find an option for myself. Over the years my finger contractures progressed slowly, and I was able to adapt the use of my hands slowly, too, to match the changes that occurred, and I was able to work through it. The danger was that in the crevices of my fingers the skin was soft and would tear easily. In a matter of seconds I could rip the skin, sometimes to the point of exposing the tendon, opening up for infection to set in. Once I got an infection it affected everything, my teaching, my work around the farm, the pain and the amount of time it would take to heal such soft and often damp skin. Numerous doctors agreed that what worked for Paul would not work for me and their best option to prevent those dangerous tears was to amputate below the second knuckle, my answer was a resounding "no thank you!". I was eventually referred to the Philadelphia Hand to Shoulder Center and Dr. A. Lee Osterman, a world-renowned hand specialist, who agreed that what worked for Paul would not work for me, but he had another idea. His idea was to straighten and fuse my pointer and middle finger with a screw, and then wire my ring and pinky finger joints into a slightly curved, gripping, position. Then he wanted to take the Flexor Digitorum Superficialis, the same FDS that was used in Paul's surgery, from my ring finger and reroute it to the Intrinsic Flexors/Opponens of the thumb, thus restoring the three jaw chuck and pincer pinch grip of that hand. After two surgeries, one in November and another in December, I had to reteach my brain that what used to make my ring finger bend now pulled my thumb over to a more usable position, think of it as making a cup in the palm of my hand. That was all on my left hand and I had planned on doing my right hand the same way as soon as college was over for the spring semester but, due to the COVID-19 pandemic that surgery has been postponed.

A Call to Help

I tell my story because, like I said before, not everyone is affected the same way so the treatment for everyone might not be the same. Maybe something that worked for me would spark an idea to help you or to have your doctor help you. We create a better team when we can share our experiences. You see it every year in the Deater Foundation newsletter, ideas, suggestions, personal experiences, and stories that uplift and inspire hope. As a family we have been doing this for generations, but I am extremely proud of this group of individuals who have come together and helped, really helped, people from all around the world.

Of course, the Deater Foundation cannot wholly operate on hope, we need your support. I know that the economy isn't the best right now and unemployment is rampant but if you are able to give the Deater Foundation would greatly appreciate your gift and I know that the DFI board of directors works diligently to use those donations to make the greatest impact possible towards finding a cure for this disease. If you are unable to make a monetary donation please consider helping in other ways, like sharing a story, sharing the website (deaterfoundation.org) or even just liking and sharing our Facebook page (Deater Foundation, Inc), who knows how far we can reach and how many people we could help just by you sharing.

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Help for Hands by Christine Deater Christensen

HSAN1 causes a significant amount of hand deformity. Through the website Amputee Coalition, I started receiving a magazine called In Motion. In the very first issue I received there happened to be an article on hand prosthetics. The company Naked Prosthetics custom builds an apparatus that fits over your wrist and works with the digits you have. The prosthetic looks amazing and shows hands that look like mine. I am working with my prosthetist to see if I qualify for one. I do not know the cost yet, but if/when I get to that next step, I will share more information on the Deater Foundation website.

Company name: Naked Prosthetics
Website: npdevices.com
Email: info@npdevices.com
Phone: 888-977-6693

Treatment Offers Hope

A newspaper feature to educate the public about HSAN1 in one family

"Thomas Deater went off to fight the Civil War with ulcers on his feet." So begins an article published in the Wilkes-Barre Citizens' Voice and the Scranton Times-Tribune March 29,2020.

Author Jamie Talan sourced family oral history written down by Harvey Deater, genealogy research by Larry Deater, a personal interview with David Elston, and medical investigation by Dr. Florian Eichler to write about the history of HSAN1 in the Deater family. Ms Talan credits the Deater family with pursuing research regarding HSAN1 from prior to 1939, the date of the first publication on the disease in the family, until the present day. The full article is available on the Deater Foundation, Inc. website at www.deaterfoundation.org

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HSAN1/MacTel Linkage

In September of 2019, research was published in *The New England Journal of Medicine* confirming that two of the genetic variants that are known to cause HSAN1 also cause the eye disease, Macular Telangiectasia type 2 (MacTel). This research was performed under the direction of Dr. Paul Bernstein (Moran Eye Center in Salt Lake City, UT) and involved a highly sensitive imaging technology, called FLIO, which is only available for use in the United States at this specific eye institute. Martin Friedlander, MD, PhD, of the Lowey Eye Institute was the senior author on the study which was supported by the Lowey Institute.

A handful of Deater family members volunteered to fly to Salt Lake City and participate in this study, along with other participants with and without HSAN1. The data obtained was helpful in determining the associated linkage between the two diseases. Since HSAN1 is known to cause elevated levels of neurotoxic deoxysphingolipids that accumulate in the body, it is thought that these same neurotoxic compounds could also be responsible for the macular damage seen in patients with MacTel. This study is the first to describe the linkage between systemically low serine levels and increased deoxysphingolipid levels as being potential risk factors for developing MacTel. Importantly, the research concluded "that elevated deoxysphingolipid levels can cause macular disease in the broader population of patients with macular telangiectasia type 2, as well as in patients with HSAN1."

The full paper is titled, "Serine and Lipid Metabolism in Macular Disease and Peripheral Neuropathy" and can be found on the DFI website.

Natural History and Biomarkers in Hereditary Sensory Neuropathy Type 1

A collaboration between the University of Massachusetts Medical School and Massachusetts General Hospital to study the progression of HSAN1 in individuals over time resulted in an important paper (Muscle & Nerve, 2015) chronicling how the disease progresses the variation of progression. Questionnaires, physical examination, various tests, and skin biopsies were utilized in gathering information from 23 affected individuals, many from the Deater family.

Of particular interest was the conclusion, *"HSAN1 Is a misnomer, at least for the most common SPTLC1 mutations. Motor axonopathy was severe as assessed by symptoms, signs, and electrophysiological study, whereas autonomic neuropathy was scant."* This study also recognized that, because of the insidious gradual onset, *"HSAN1 is actually a pediatric-onset disease, and the optimal timing for therapeutic intervention is likely to be in childhood."*

The Deater Foundation helped to fund this research; the full study is available on its website.

***Easy ways for you to help*!**
*If you order anything from Amazon, sign up for **Amazon Smile** and choose **Deater Foundation, Inc**. to receive a donation from Amazon.
*The **Facebook Birthday Fundraiser** lets people know your favorite charity and right now 100% of the donations go to your designated **Deater Foundation**!
*If your company contributes to **United Way** or has a **Matching Gift Program** be sure to designate **Deater Foundation, Inc.** as a recipient.

The Deater Foundation
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