Deater Foundation, Inc.
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The Deater Foundation, Inc.
Newsletter May 2024
Advancing research to discover treatment and a cure for Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1)

The Deater Foundation, Inc. (DFI) has a long history of collaborative support with Dr. Robert H. Brown, Jr. Dr. Brown has forged a strong personal connection with the Deater family and the Deater Foundation has for many years provided financial support to his laboratory and to other projects on his recommendation. The funding for several symposiums and the donation to Dr. Dunn's laboratory at the Uniformed Services University for the nitrogen generator have all worked to further research in HSAN1.

In 2023 DFI awarded a $30,000.00 grant to Dr. Brown's lab to provide support for Erinn Ives, a research associate with a degree in biology who handles many experiments and also manages the colony of HSAN1 mice. Another member of the team, Sushmita Nayak, is an "outstanding PhD candidate" in Dr. Brown's lab who works half time on HSAN1 studies. She has excellent organizational skills and extensive prior experience in studies of stem cells in cell culture.

Working in Dr. Brown's lab full time through the summer is Justin Lee, a post-doc who completed his degree in Dr. Brown's lab. Dr. Lee published a new way to examine the transport function of nerve fibers (axons) and showed that this approach provides very sensitive early detection of benefit from treatment.

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

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

It is a pleasure to provide a brief update on the status of our investigations of HSAN1 in my laboratory. Let me say first that we are fortunate to have a strong team engaged in these studies.

Our studies now are focused in three areas:

First, we have greatly expanded the colony of mice that have the Deater HSAN1 mutation (SPTLC1 gene, C133Y) knocked into the mouse genome. You will recall that these mice were generated by a previous doctoral student, Huiya Yang. Sushmita and Erinn have now characterized function of the mice for more than a year. It is reassuring that we see a clear molecular phenotype for HSAN1 in the mice. These results have been achieved through collaboration with Dr. Teresa Dunn. The molecular findings are weakly apparent at three months but very distinct by 6 months of age. As was reported by the Jackson Laboratories using the C133W HSAN1 mice, our C133Y mice show thus far only minimal sensory abnormalities. We do find some sensory deficits but are devoting considerable effort to enhancing the sensitivity of the sensory examination. For this purpose, we have acquired new quantitative sensory testing apparatus for mice. We are also exploring manipulating the animal diet to exacerbate the clinical findings.

Second, we have continued to explore the use of antisense oligonucleotides (ASO) to suppress the HSAN1 gene. Sushmita has reproduced the findings from Huiya Yang that our ASOs do in fact suppress the gene in Deater fibroblasts in cell culture. Importantly, we now have studies underway to look at this gene suppression in the C133Y mice. For this purpose, we have generated a large colony of mice that will allow us to study the impact of the ASO at different ages in treated versus untreated mice. This comparison of treated versus untreated is focusing on suppression of the gene in two tissues - the spinal cord with the sensory ganglia and the liver. We are hopeful that this experiment will help us define more precisely the source of the deoxysphingolipids which are one of the toxic hallmarks of this disease. We are also running a parallel study of the same experiment with dietary manipulations that may enhance the clinical and molecular findings. Here again, this very large study is possible because of the collaboration with Teresa Dunn. We expect to have data from this study in late spring or early summer.

Third, with Justin Lee, we are exploring two new avenues. One is to try to develop stem cell cultures with the C133Y mutation from which we can generate sensory neurons, as well as other types of neurons should we desire them (e.g., motor neurons). Another path forward, drawing upon Justin's expertise in imaging axonal transport in motor neurons, is to determine if there are ways to image the integrity of sensory neurons. Such an approach would theoretically allow repetitive testing without having to do nerve biopsies. As you know, some estimates of sensory nerve function are also possible using electrophysiological measures, a route we are not presently investigating but may turn to in the future.

In summary, it is a pleasure to report that we have a full head of steam in this project. The results of the current, large trial of ASO therapy will be important in ascertaining the feasibility of this approach for treating HSAN1 preclinically and eventually clinically.

GENERATIONS OF JOY
by Eileen Deater Ellsworth

I have lived through three quarters of a century; long enough to have observed three generations of HSAN affected people. My father was a member of that first generation. He was one of twelve siblings, and his symptoms became apparent in his mid-teens, sometime before 1920. In 1941 he had both his feet amputated due to bone infection. Eventually, it turned out that seven of the twelve siblings had "the disease." They called it the Deater Disease because it seemed unique to their family. As far as anyone knows, it had actually begun with my grandfather and a few of his siblings, but in my childhood memories the disease seemed to belong to my Dad and uncles and aunts.

I was born in 1949, my parents' first child, and the twentieth of thirty-five first cousins born to that first generation. I remember, when I was still very young, coming to the realization that all daddies didn't have artificial legs. For my Dad, and the siblings with the disease there were hard times of infections, growing weakness and disabilities. In their family, though, there was something deeper and far greater that held them together. There was great joy. They helped and cared for each other. They prayed together. They were bound together in an incredible bond of love!

For me, being part of the Deater family was a wonderful thing! We were a close-knit bunch! I grew up in a world of family love and a gang of cousin-friends. We had annual reunions and Christmas parties, as well as clambakes, Memorial Day picnics, weddings, funerals, holidays, vacations, and weekend family get-togethers. We cousins had such good times together! Of course, the effects and concerns of the disease were always there, too, especially among that first generation. As adults they had conversations about its issues and mysteries. As children, we had questions that had no answers, but we also had a world full of fun and distractions to occupy our minds.

The second generation was my generation. My oldest cousins were much older than I was. I had second cousins who were my age. As time passed and we all were growing older, we children of the affected first-generation were aware that the disease could be passed down, but in my house we didn't talk about that. There were no cures, no treatments, so my parents quietly watched and hoped we would not be affected.

I was in my mid-teens and no one in my generation had shown any symptoms. There was a quiet, growing hope that the disease might not be passed on at all until one of my second cousins was diagnosed. It was a crushing blow to the family, but it didn't destroy us. That bond of love held strong. Our prayers were renewed with great intensity. Hope and joy overcame. I was diagnosed a few years later, and after that another cousin, and then another…

At the same time something else was happening. Medical science was making great strides in understanding genetics and researchers began studying our disease. Our family bond of love prompted us, some with the disease and some without the disease, to volunteer for studies. Over time, knowledge of the cause and pathology of this disease we now know as HSAN type 1 has really grown. My generation has been a generation of discovery. Identifying the chromosome and then the gene that causes the disease were huge steps and we all rejoiced.

I have learned that life does not always go the way you want it to go, but it can still be good. There are all kinds of diseases, accidents, and bad choices that shatter your dreams and plans. In the end you only ever have two choices going forward. You can sit in a corner and

wallow in self-pity and bitterness, or you can build new plans and dreams, give thanks for the things you can do, and find joy in the good things the Lord has blessed you with. As I sit here in my wheelchair, typing with the eraser ends of two pencils held in my fists, I can smile, even laugh, because I am filled with joy! My life has been good!

I look forward with hope for the third and fourth generations; the generations of my own children and grandchildren. They only know of those years of mystery and not knowing through my stories, and yet their road is still so hard. There is knowledge but not answers, and the research road is a terribly slow one in a world that seems to be going so fast in other ways. I see them adjusting their plans and dreams, finding the things they can do. I see them praying, helping each other, wrapped together in that bond of love. I see them filled with joy, and I know that God is good.

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HSAN1 Registry

Jon Ellsworth

The HSAN1 Registry is a collaboration between the Deater Foundation and the University of Massachusetts Chan Medical School (UMass).

As someone who is directly impacted by HSAN1-me and my kids- I view the registry as a vital tool in research opportunities. 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 at UMass, 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 a way we can connect with researchers when they seek information or look for participants in future trials.

If you or someone you know has HSAN1, I encourage you to register today! The information is securely held on UMass servers. For information and to register, visit DFI's website: godfi.org

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You Can Help. Please Donate.

Research is expensive and careful, methodical, and replicable research is painstakingly slow. Except for minimal PayPal processing fees, the Deater Foundation spends every donated dollar on furthering research. We invite you to partner with us on our quest for a cure for HSAN1!

SPLTC1 and Childhood onset amyotrophic lateral sclerosis (ALS)

Hereditary sensory and autonomic neuropathy type 1 (HSAN1) is caused by a mutation in the SPLTC1 gene which provides instructions for making one part (subunit) of an enzyme called serine palmitoyltransferase (SPT). The SPT enzyme is involved in making certain fats called sphingolipids. Sphingolipids are important components of cell membranes that influence many cell functions. The SPT enzyme initiates the first step of sphingolipid production, in which the molecules serine and palmitoyl CoA combine to form a molecule called ketodihydrosphingosine. Additional chemical reactions convert ketodihydrosphingosine into various types of sphingolipids. HSAN1 mutations cause the enzyme to produce **atypical** and harmful versions of sphingolipids.

Dr. Carsten Bönnemann at the National Institute of Neurological Disorders and Stroke examined a young patient with symptoms of amyotrophic lateral sclerosis (ALS) but with early-age onset and slower progression. In total, 11 patients with similar symptoms were identified. To understand the underlying cause of this distinct form of ALS, Dr. Bönnemann's team analyzed their DNA . They found all patients had changes in the SPLTC1 gene but showed no signs of the harmful sphingolipids seen in HSAN1.

With the help of Dr. Teresa Dunn, (Uniformed Services University), who has studied sphingolipids for decades, and Dr. Thorsten Hornemann (University of Zurich), it was determined that the levels of **typical** sphingolipids were abnormally high. This suggested that the ALS mutations enhanced SPT activity. Experiments showed that the mutations causing ALS prevent another protein from inhibiting SPT activity.

To test this idea, the team created small interfering strands of RNA designed to turn off the mutant SPLTC1 genes. Experiments on the patients' skin cells showed that these RNA strands reduced the levels of SPLTC1 gene activity and restored sphingosine levels to normal.

Dr. Bönnemann said, "These preliminary results suggest that we may be able to use a precision gene silencing strategy to treat patients with this type of ALS. .. Our ultimate goal is to translate these ideas into effective treatments for our patients who currently have no therapeutic options."

This study was supported in part by the Deater Foundation.

Mohassel, P. et al., Childhood Amyotrophic Lateral Sclerosis Caused by Excess Sphingolipid Synthesis. Nature Medicine, May 31, 2021

Mass Spectrometer for Dr. Teresa Dunn's Laboratory

In 2022 DFI learned that Dr. Dunn-Giroux's Lab at the Uniformed Services University had the opportunity to receive a Mass Spectrometer from another department for dedicated use in her Lab. It required a nitrogen generator to be functional. DFI donated $25,000.00 to the Uniformed Services University Gift Program. " The Mass Spec has been delivered and tested and the renovations to the space in the basic instrumentation center have been approved, budgeted, and are slated to begin soon. Although moving slowly, we are getting close to having a dedicated instrument for analyzing samples from Dr. Brown, which will facilitate the studies."

Deater Foundation Inc Treasurer's Report

Balance as of 4/1/23	$62,876.29
Income:	
Contributions 4/1/23 to 12/31/23	8,562.43
Interest 4/1/23 to 12/31/23	9.88
Contributions 1/1/24 to 3/31/24	4,395.00
Interest 1/1/24 to 3/31/24	1.78
Total Income	12,969.09
Expense:	
Deater Fund @ UMass (July)	30,000.00
Lionel Lynner Website Maintenance 8/12/23	400.00
Teresa Dunn-nitrogen generator (Oct)	25,000.00
PayPal Service Charges	- 5.56
Total Expense	55,405.56
Balance as of 3/31/24	$20,439.82

Please note – The check for $25,000.00 made out to Dept of Treasury for Teresa Dunn to acquire the nitrogen-generator for the mass spectrometer was dated and mailed out on 10/11/23. The donation has been approved but the check has not yet been cashed.

Charcot-Marie-Tooth (CMT) in the News

Iconic country music singer Alan Jackson revealed that he has been diagnosed with Charcot-Marie-Tooth disease. CMT hereditary neuropathy refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy. Individuals with CMT have progressive loss of muscle tissue and loss of sensation in the arms and legs. HSAN1 is not recognized as one of the CMT disorders because its specific genetic mutation is not one of the 40 + mutations of CMT. However, prior to genetic testing, many people with HSAN1 were diagnosed with CMT based on their symptoms. Mr. Jackson has a father, grandmother, and sister with the same diagnosis. We wish Mr. Jackson well. Perhaps his celebrity will bring more attention to inherited neuropathies, and perhaps more funding.

Raise the Region Fundraiser

Eric Newcomer

Thank you to everyone who donated to Deater Foundation during Raise the Region and a special welcome to everyone receiving our newsletter for the first time because of your generosity.

On March 13th and 14th this year Deater Foundation had the opportunity to participate in a 30 - hour fundraising event for non-profits in central Pennsylvania, Deater Foundation is in Union County, one of the seven counties served by this program. This event is hosted by the First Community Foundation Partnership of Pennsylvania, an organization that helps philanthropists grow their contributions and reinvest the gains back into our region. Deater Foundation was one of the 350 organizations that shared in a total of $2,343,179 raised by 7,853 donors and we raised $3,425 from 34 donors. Cindy and I were able to go to the kickoff event where we met many other nonprofits and lots of donors from previous years, but we had the most fun early the next morning. We were on our local news station, WNEP, for their first broadcast at 4:30 am and every half hour after that until 7 am. Even though it was early we again met numerous other groups trying to get on TV and a few of the people from Blaise Alexander Family dealerships, that donated $175,000 in stretch funds to the pot. It was amazing how many people we ended up knowing that watch the news so early in the morning, I think we all got messages from someone we knew who saw us on TV. Plus, it was a great opportunity, and we are looking forward to doing it again next year, hopefully with some new ways to get more attention and raise some more money for DFI. In the picture going left to right is my daughter Alexis who had to be at college for a test later that morning, myself, our friend Becca, my daughter Lindsey, my wife Cindy, and our friend Daria.

Connect with the HSAN1 community on Facebook by joining **@ Deater Foundation, Inc.**

MacTel Update

Tami Murphy

Macular telangiectasia type 2 (MacTel) is a rare, slowly progressive degenerative disease of the macula of the eye that results in gradual loss of central vision. The Lowy Medical Research Institute first identified a potential link between HSAN1 and MacTel. It was initially believed that MacTel was a disease of blood vessels in the retina. MacTel is now understood to be, first and foremost, a disease that affects the neurons in the eye. Many members of the Deater family have participated in recent MacTel research studies to try to help clarify this connection. Recent research updates on the possible HSAN1-MacTel connection were submitted by Dr. Mari Gantner with the Lowy Medical Research Institute. (citations below).

The first paper described findings in a group of HSAN1 patients (mostly in the UK) with known SPTLC1 or SPTLC2 mutations in which none of the patients showed clinical evidence of MacTel. These findings could indicate that the connection between MacTel and HSAN1 is more complex than just an association with specific genetic variants.

The second paper outlined differences in blood metabolites between HSAN1 and MacTel patients. Both had elevated deoxysphingolipid levels. MacTel patients had low serine and glycine levels, but elevated alanine levels (similar to what is seen in type-2 diabetic individuals). HSAN1 patients had the opposite: elevated circulating serine and glycine levels with decreased alanine levels, along with a reduction in ceramides and sphingomyelin (whereas the other complex sphingolipids were not generally affected). Interestingly, this could suggest that supplementation of certain sphingolipids might be of therapeutic benefit to HSAN1 patients, perhaps in addition to serine. Patients with both HSAN1 and MacTel had the most significant decrease in sphingomyelin levels.
“Blood metabolite serine and sphingolipid levels don’t appear to be sufficient to explain why some HSAN1 patients have MacTel, while others do not. We are still very actively trying to figure out why some HSAN1 patients develop MacTel while others do not.”

Dr. Gantner and her team are wrapping up a study evaluating high-dose serine supplementation in MacTel patients (as was previously done with HSAN1 patients) and/or fenofibrate to see how these treatments could alter deoxysphingolipids and other metabolite levels. They hope to learn what might be the best approach to correcting the metabolic changes in MacTel patients (without SPTLC1 variants). This will hopefully also be informative for HSAN1 patients.

Rodrigues FG, Pipis M, Heeren TFC, Fruttiger M, Gantner M, Vermeirsch S, Okada M, Friedlander M, Reilly MM, Egan C. Description of a patient cohort with Hereditary Sensory Neuropathy type 1 without retinal disease Macular Telangiectasia type 2 - implications for retinal screening in HSN1. J Peripher Nerv Syst. 2022 Sep;27(3):215-224.

Green CR, Bonelli R, Ansell BRE, Tzaridis S, Handzlik MK, McGregor GH, Hart B, Trombley J, Reilly MM, Bernstein PS, Egan C, Fruttiger M, Wallace M, Bahlo M, Friedlander M, Metallo CM, Gantner ML. Divergent amino acid and sphingolipid metabolism in patients with inherited neuro-retinal disease. Mol Metab. 2023 Jun;72:101716.

Diabetic Neuropathy and L-serine Supplementation

Deoxysphingolipids are sphingolipids toxic to nerves. They are associated with obesity and diabetic neuropathy and have been linked to severity of functional peripheral neuropathies (and HSAN1). L-serine supplementation can reduce deoxysphingolipid accumulation and improve insulin sensitivity and sensory nerve speed. This recent study led by Dr. Florian Eichler tested a mouse model to determine the extent of functional neuropathy progression over time. With supplementation of L-serine in mice with diabetes mellites, toxic deoxysphingolipids were suppressed long-term in blood and tissue. Functional neuropathy and sensory modalities were significantly improved. However, other results suggest that the neuropathy was ongoing. The results indicate that despite significant functional improvements L-serine does not prevent degenerative changes at the structural level, pointing to other processes, such as hyperglycemia, that persist despite deoxysphingolipid reduction.

Long-term effects of l-serine supplementation upon a mouse model of diabetic neuropathy
Chuying Xia, Saranya Suriyanarayanan, Yi Gong, Vera Fridman, Martin Selig, Jia Li, Seward Rutkove, Thorsten Hornemann, Florian Eichler. J Diabetes Complications 2023 Feb; 37(2):108383.doi;101016/j.jdiacomp.2022-108383 Epub 2022 Dec 10

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An Alternate View of Sphingolipid Pathology in HSAN1

Disruptions in sphingolipid metabolism are a common pathogenic hallmark of many disorders, such as cancer, diabetes, and neurodegenerative diseases. Often, the symptoms of these diseases are thought to be brought about by the accumulation of toxic intermediates or byproducts. In the case of HSAN1, it is thought that the production and aggregation of neurotoxic deoxysphingolipids, which cannot be further built upon or degraded, contribute to the neuropathy commonly associated with this disease.

The work of Zhang et al. established a *C. elegans* (worm) model of HSAN1 with an SPTLC1 mutation equivalent to human C133W. In this organism, it was shown that the HSAN1 mutation resulted in a loss of function effect, rather than through an accumulation of toxic byproduct. This loss may bring about a decrease in downstream production of complex sphingolipids, specifically glucosylceramide.

The findings using this *C. elegans* model of HSAN1 could have implications for screening potential new therapeutic compounds for use in HSAN1, as well as in additional neurological conditions and inherited metabolic disorders.

A Model of Hereditary Sensory and Autonomic Neuropathy Type 1 Reveals a Role of Glycosphingolipids in Neuronal Polarity
Mengqiao Cui, Rong Ying, Xue Jiang, Gang Li, Xuanjun Zhang, Jun Zheng, Kin Yip Tam, Bin Liang, Anbing Shi, Verena Göbel and Hongjie Zhang
Journal of Neuroscience 17 July 2019, 39 (29) 5816-5834

The **Deater Family Reunion** will be held on

Saturday, July 20 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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